Adverse drug reaction-related hospitalisation in Ethiopia

A thesis submitted in accordance with the requirements of the University of Tasmania for the degree of Doctor of Philosophy

By

Mulugeta Angamo (BPharm, MSc ClinPharm)

Division of Pharmacy, School of Medicine, College of Health and Medicine

University of Tasmania, Hobart, Australia

November 2018

Declaration of originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

Mulugeta Angamo

November 2018

Statement of authority of access

This thesis is not to be made available for loan or copying for two years following the date this statement was signed. Following that time the thesis may be made available for loan and limited copying and communication in accordance with the Copyright Act 1968.

Mulugeta Angamo

November 2018

Statement of ethical conduct

The research associated with this thesis abides by the Australian codes on human and animal experimentation, the guidelines by the Australian National Ethics and Institutional Biosafety Committees of the University. All research involving patients hospitalised with adverse drug reactions was conducted under the approval of the Tasmanian Human Research Ethics Committee (reference number H0014718) and the Jimma University Institutional Review Board (reference number RPGC/58/2015).

Mulugeta Angamo

November 2018

Statement of co-authorship

Given that this thesis is presented as a sequence of published, in press or submitted manuscripts, a statement of co-authorship is provided for each chapter. Due to this thesis format, some repetition is to be expected.

The following individuals and organisations contributed to the publication or preparation of the work undertaken as part of this thesis.

Candidate: Mulugeta Tarekegn Angamo

Author 1: Colin Michael Curtain[1]

Author 2: Leanne Chalmers[1]

Author 3: Daniel Yilma[2]

Author 4: Luke Bereznicki[1]

[1] Division of Pharmacy, School of Medicine, College of Health and Medicine, University of Tasmania, Hobart, Tasmania, Australia

[2] Department of Internal Medicine, Jimma Institute of Health, Jimma University, Jimma, Oromia, Ethiopia

Publications

All publications, manuscripts in press and submitted resulted from work described in this thesis.

Peer-reviewed Journal Publications

1. Angamo MT, Chalmers L, Curtain CM, Bereznicki LR. Adverse-drug-reaction-related hospitalisations in developed and developing countries: A review of prevalence and contributing factors. Drug Saf. 2016;39 (9):847-57. doi: 10.1007/s40264-016-0444-7.

Located in Chapter 2: *Candidate was the primary author; who in conjunction with authors 1, 2 and 4 conceived and designed the study. Candidate undertook all data collection, analysis and drafting of the manuscript. Authors 1, 2 and 4 provided input into the writing of the research article.*

2. Angamo MT, Curtain CM, Chalmers L, Yilma D, Bereznicki L. Predictors of adverse drug reaction-related hospitalisation in Southwest Ethiopia: A prospective cross-sectional study. *PLoS One.* 2017; 12(10):e0186631. doi:10.1371/journal.pone.0186631

Located in Chapter 3: *Candidate was the primary author; who in conjunction with authors 1-4 contributed to the study design and development. The candidate drafted the manuscript. All authors provided input into the writing of the research article.*

3. Angamo MT, Chalmers L, Curtain CM, Yilma D, Bereznicki L. Mortality from adverse drug reaction-related hospitalisations in southwest Ethiopia: A cross-sectional study. J Clin Pharm Ther. 2017. https://doi.org/10.1111/jcpt.12702.

Located in Chapter 4: *Candidate was the primary author; who in conjunction with authors 1, 2 and 4 conceived and designed the study. Candidate undertook all data collection, analysis and drafting of the manuscript. All authors provided input into the writing of the research article.*

4. Angamo MT, Curtain CM, Chalmers L, Yilma D, Bereznicki L. Drug-induced hepatotoxicity-related hospitalisation: Patterns, severity and implicated drugs (under review)

Located in Chapter 5: *Candidate was the primary author; who in conjunction with authors 1-4 contributed to the study design and development. The candidate drafted the manuscript. All authors provided input into the writing of the research article.*

Conference abstracts

1. Angamo MT, Chalmers L, Curtain CM, Bereznicki LR. Adverse-drug-reaction-related hospitalisations in developed and developing countries: A review of prevalence and contributing factors. Ethiopian Public Health Institute Third Scientific Congress. Addis Ababa, Ethiopia, October 27-29, 2016.
2. Angamo MT, Curtain CM, Chalmers L, Yilma D, Bereznicki L. Predictors of adverse drug reaction-related hospitalisation in Southwest Ethiopia: A prospective cross-sectional study. University of Tasmania Annual Graduate Research Conference 2017. Hobart, September, 2017
3. Angamo MT, Curtain CM, Chalmers L, Yilma D, Bereznicki L. Predictors of adverse drug reaction-related hospitalisation in Southwest Ethiopia: A prospective cross-sectional study. Australasian Pharmaceutical Science Association (APSA) Annual Conference 2017. Brisbane, December 5-8, 2017

We the undersigned agree with the above stated, "proportion of work undertaken" for each of the above published or under review peer-reviewed manuscripts contributing to this thesis:

Candidate (School of Medicine, University of Tasmania): Mulugeta Angamo

Author 1 (School of Medicine, University of Tasmania):

Author 2 (School of Medicine, University of Tasmania):

Author 3 (School of Medicine, Jimma University):

Author 4 (School of Medicine, University of Tasmania):

We the undersigned agree with the above stated "proportion of work undertaken" for each of the above published (r submitted) peer-reviewed manuscripts c trib uting to this thesis:

Signed

Name Professor Luke Bereznicki

Supervisor

School of Medicine

University of Tasmania

Date: 20th November 2018

Signed

Name Prof Ben Canny

Head of School

School of Medicine

University of Tasmania

Date: 20th November 2018

Acknowledgements

This project was supported by the Division of Pharmacy, College of Health and Medicine, University of Tasmania. I am grateful to the University of Tasmania for awarding me an International Postgraduate Research Scholarship (IPRS) and Tasmania Graduate Research Scholarship (TGRS) to undertake my study.

I would like to express my sincere gratitude to my primary supervisor, Professor Luke Bereznicki, for providing me with the opportunity to work on an interesting project that I believe will show the clinical burden and risk factors of adverse drug reaction-related hospitalisation in a resource limited setting, for his knowledge, motivation, suggestions, and understanding. His extraordinary supervision and intuitive comments assisted me in all the time of research design, data analysis and writing of this thesis. Without your contribution to resolving technical and administration issues, successful completion of the project would not have been possible.

I express my heartfelt gratitude to Dr. Leanne Chalmers for her encouragement, insightful comments and patience. I especially thank Dr. Leanne Chalmers for her critical remarks and suggestions throughout the design and development of all the contents of my PhD thesis.

I owe my gratitude to Dr. Colin Curtain for developing the Access database and assisting me in handling and processing the data. I would like to thank Dr. Colin Curtain for his critical remarks and suggestions throughout the data analysis of the manuscripts in this PhD thesis.

I would like to pass my gratitude onto Dr. Daniel Yilma for his active participation in the review and ADR causality assessment process and writing of each manuscript of this project.

I would like to thank Mr. Tsegaye Melaku, Mr. Getandale Zeleke, Mr. Temesgen Mulugeta, and Mr. Mengist Awoke, who assisted me during data collection for this project. Without your enthusiasm and commitment to the project, none of this would have been possible.

I would like to thank the clinical pharmacy Masters students, medical doctors, medical interns, hospital pharmacists, nurses, hospital managers, academic staff of the School of Pharmacy and all my friends, Jimma University, for their assistance during the recruitment and follow-up, organising access to patients' medical records, sharing your office and encouragement during the study. I am grateful to all study participants for their participation.

I would like to thank all the Division of Pharmacy staff and PhD students for their encouragement and support over the course of my study and to all my friends who have helped me in innumerable ways over the past four years. We had unforgettable times together that I will value.

My wife, Bizuayehu Gebreyohannes, my sons, Yeabsera and Betsegaw, and my daughter, Beimnet, gave me a purpose for working harder and a sense of determination. My parents, Ato Tarekegn Angamo and Wizero Adanech Bule, and my borther and sisters have all the time been exceptionally helpful to my education in your prayers.

Above all, I would like to thank my ALMIGHTY GOD for his mercy, grace and love throughout my journey.

Abbreviations and acronyms

ACE	Angiotensin Converting Enzymes
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AKI	Acute Kidney Injury
AIDS	Acquired Immune Deficiency Syndrome
ALF	Acute Liver Failure
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
Anti-TB	Anti-Tuberculosis
AOR	Adjusted Odds Ratio
ART	Antiretroviral Therapy
AST	Aspartate Transaminase
AUROC	Area Under Receiver Operator Curve
BARDI	Bayesian Adverse Reaction Diagnostic Instrument
BUN	Blood Urea Nitrogen
CAD	Canadian Dollar
CCI	Charlson Comorbidity Index
CDSS	Clinical Decision Support Systems
CPOE	Computerised Physician Order Entry

CYP3A4	Cytochrome P450 3A4
DIH	Drug-Induced Hepatotoxicity
DoTS	Dose Relatedness, Timing, and Patient Susceptibility
eGFR	estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FMHACA	Food, Medcine, Health Adminstration and Control Authority
GI	Gastrointestinal
HAD	Health Development Army
HEP	Health Extension Packages
HEW	Health Extension Workers
HIV	Human Immunodeficiency Virus
IgE	Immunoglobulin E
IQR	Interquartile Range
LOS	Length of Stay
MAI	Medication Appropriateness Index
ME	Medication Error
NSAID	Non-Steroidal Anti-inflammatory Drugs
OTC	Over the Counter
PV	Pharmacovigilance
RCT	Randomised Controlled Trial

ROC	Receiver Operator Curve
TDM	Therapeutic Drug Monitoring
TB	Tuberculosis
START	Screening Tool to Alert Doctors to Right Treatment
STOPP	Screening Tool of Older Persons' Potentially Inappropriate Prescriptions
UMC	Uppsala Monitoring Centre
USD	United States Dollar
WHO	World Health Organisation
WHO-UMC	World Health Organisation Uppsala Monitoring Centre

Abstract

Adverse drug reactions (ADRs) are an important healthcare problem frequently associated with significant morbidity, hospitalisation and mortality. Globally, the prevalence of ADR-related hospitalisation and mortality vary from 0.2% to 54.5% and 0.1% to 10.0%, respectively. Severe ADRs are important reason for admission to intensive care unit and extensions of hospital stay in approximately one-fifth of overall ADR-related admissions. Overall, the rates of ADR-related hospital admissions and mortality are comparable between developed and developing countries. However, there are marked differences between developed and developing countries with regard to the nature of the ADRs implicated in hospital admissions and the mortality rate. In addition, there are some important differences in risk factors contributing to ADR-related hospital admissions and mortality due to the differences in population socio-demographics, disease characteristics, drug therapy used, healthcare systems and ethnic origins.

In Ethiopia, a developing country, there are number of factors thought to increase the risk of ADR-related hospital admission. These include, but are not limited to, a greater proportion of patients who take anti-tubercular (anti-TB) drugs and antiretroviral therapy (ART), a high prevalence of malnutrition and anaemia, a higher prevalence of concomitant anti-TB drugs and ART use, and widespread use of traditional remedies. In addition, there is a higher proportion of the slow acetylator phenotype among patients on ART and anti-TB drugs that increases susceptibility to ADRs. There is growing attention to chronic disease management with new and complex therapies in ambulatory care clinics, where there are higher rates of drug-related problems and irrational use of medicines that could lead to drug-related harm. Unlike developed countries, there is substantial all-cause mortality rate among patients presenting to emergency departments, a high rate of mortality among HIV/TB co-infected patients on drug therapy, a less health-literate population and a lesser ability to provide healthcare. Moreover,

there are increasing rates of concurrent infectious and non-communicable diseases demanding multiple medications with potential drug interactions.

The majority of studies focussing on risk factors for ADR-related hospitalisation and mortality have been conducted in developed countries. In Ethiopia, to our knowledge, there are no studies reporting on the prevalence and risk factors associated with ADR-related hospitalisation, or the mortality rate attributable to ADRs in patients presenting to hospital. The limited information available in the Ethiopian setting, the presence of multiple factors suspected to increase the risk of ADR-related admissions and evidence of a substantial burden of ADR-related admissions and mortality in other settings provided the impetus for this study. Determining the magnitude of ADR-related hospitalisation and mortality and identifying factors contributing to ADRs for community-based patients are crucial in understanding the extent of the problem and developing preventive strategies to decrease the clinical and economic burden. Therefore, the main aims of the body of work presented in this thesis were to identify ADRs responsible for ADR-related hospital admissions; investigate the medications and other risk factors associated with the ADRs; and to determine their severity, preventability, clinical presentation and outcomes.

Due to the absence of similar studies in Ethiopian patients, we began by reviewing the existing literature on the prevalence and contributing factors of ADR-related hospitalisations in developed and developing countries. From 43 relevant publications identified through systematic review, the median (with interquartile range (IQR)) prevalence of ADR-related hospitalisations in developed and developing countries were 6.3% (3.3-11.0%) and 5.5% (1.1-16.9%), respectively. Similarly, the median proportions of ADR-related mortality in developed and developing countries were 1.7% (0.7-4.8%) and 1.8% (0.8-8.0%), respectively. Older age, female gender, number of medications, renal impairment and heart failure were reported to be

associated with an increased risk for ADR-related hospitalisation in both settings, while HIV/AIDS was implicated in developing countries only. The majority of ADRs were preventable in both settings, highlighting the importance of improving medication use, particularly in vulnerable patient groups such as the elderly, patients with multiple comorbidities and, in developing countries, with HIV/AIDS.

Following review of existing literature, a prospective observational study determined the prevalence of ADR-related hospitalisation, characterised the ADR types and their preventability, characterised the implicated medications and identified predictors of ADR-related hospitalisation. This was determined through detailed review of medical records, laboratory tests and patient interviews followed by causality assessment by the Naranjo algorithm and expert consensus. Of 1,001 patients included, 103 (10.3%) were deemed to have experienced an ADR-related admission. Common ADRs responsible for hospitalisation were hepatotoxicity (35, 29.4%) followed by acute kidney injury (27, 22.7%) and electrolyte disturbances (hypokalaemia and hypocalcaemia) (13, 10.9%). The drug classes most frequently involved in ADRs were anti-TB drugs (36 patients, 35.0%), followed by ART (22 patients, 21.4%) and diuretics (19 patients, 18.4%). Body mass index (BMI) <18.5 kg/m^2 (adjusted odd ratio [AOR]=1.69; 95% confidence interval [CI]=1.10-2.62), pre-existing renal disease (AOR=2.84; 95% CI=1.38-5.85), pre-existing liver disease (AOR=2.61; 95% CI=1.38-4.96), number of comorbidities ≥4 (AOR=2.09; 95% CI=1.27-3.44), number of drugs ≥6 (AOR=2.02; 95% CI=1.26-3.25) and history of previous ADRs (AOR=24.27; 95% CI=11.29-52.17) were found to be independent predictors of ADR-related hospitalisation in an ADR risk prediction model with an area under the receiver operator curve of 79.0% (95% CI 73.9%-84.1%). Most ADRs (106, 89.1%) were considered preventable.

Another component of a prospective observational study determined the prevalence of mortality attributable to ADRs in patients presenting to hospital, and identified drugs and factors associated with ADR-related mortality. Of 1,001 patients, 15 (1.5%, 95% CI=0.80-2.30%) died. Deaths were primarily due to suspected drug-induced hepatotoxicity (7 patients, 43.8%) followed by acute kidney injury (4 patients, 25.0%). Anti-TB drugs and ART together were implicated in 60% of the deaths. A bivariate comparison showed patients who died with ADRs were more likely to have pre-existing liver disease (40.0% vs. 7.0%; 95% CI=8.1-57.8%), a history of ADRs (40% vs. 1.4%; 95% CI=13.8-63.4%), a low BMI (17.6 ± 2.1 vs. 20.0 ± 2.9; 95% CI=0.9-3.9), exposure to anti-TB drugs (46.7% vs. 18.9%; 95% CI=2.3-53.1%) and ART (40.0 % vs. 7.7%; 95% CI=7.5-57.2%), a higher mean (±SD) number of medications (7.1 ± 3.3 vs. 3.8 ± 2.1; 95% CI=2.2-4.4), and Charlson Comorbidity Index (3.9 ± 2.9 vs. 1.6 ± 1.8; 95% CI=1.4-3.2) than surviving patients without ADRs.

Findings from a series of analyses in a prospective observational study led us to further characterise the clinical patterns and severity of drug-induced hepatotoxicity (DIH), which was the commonest ADR implicated in hospitalisation and mortality. In this sub-study, 674 patients with documented previous medical history and regular medication prior to hospital admission and at least one set of liver function tests were included. Of 674 patients, 35 (5.2%) were deemed to have been hospitalised due to DIH, of whom, 22 (62.9%) exhibited a cholestatic pattern, 8 (22.9%) a hepatocellular pattern and 5 (14.3%) a mixed pattern. The most frequent drug classes implicated were anti-TB drugs (21 patients, 60.0%) followed by ART (12 patients, 34.3%). More than two-thirds of the DIH cases (24, 68.6%) were severe or fatal, were mainly caused by anti-TB drugs (15, 42.9%), ART (4, 11.4%) or concomitant anti-TB/ART (6, 17.1%).

Our studies provided several novel findings regarding hospitalisation and mortality related to ADRs in Ethiopian patients. Our work revealed that the extent of ADR-related hospitalisation

in adults is an important public health problem, with a significant number of fatal ADRs in patients presenting to hospital. Commonly used drugs, such as anti-TB drugs, ART and cardiovascular agents, causing well-known reactions are the most frequently occurring ADRs in patients presenting to hospital, suggesting that strategies for their prevention should be identifiable. Conversely, the ADR-related hospitalisation risk prediction model demonstrated some ability to identify patients at higher risk for ADRs, such as patients with lower BMI, previous ADR history, renal and liver diseases, multiple comorbidities and medications. This was further augmented by an ADR preventability assessment using Schumock and Thornton's criteria, in which the majority of the ADRs were preventable provided these risk factors were reviewed and monitored closely. Therefore, consideration of the independent risk factors for ADRs identified in this study, by medical practitioners during assessment of patients at emergency and chronic care centres, might help distinguish patients who are at higher risk of ADR-related hospitalisation.

More research is needed into intervention strategies to help reduce ADR-related hospitalisation and mortality. However, key areas that demand urgent interventions based on our study findings include patients taking anti-TB drugs (isoniazid and pyrazinamide) and ART (tenofovir, efavirenz and nevirapine), with a special focus on patients with malnutrition, previous ADR history, and pre-existing renal and liver diseases. Patients with cardiovascular disorders taking furosemide, enalapril, atorvastatin, warfarin and heparin also require special consideration. Given our findings that the majority of events occurred in patients receiving treatment for infectious and non-communicable chronic diseases, ADR risk assessment and intervention strategies should focus on these groups of patients to minimise the occurrence of preventable ADR-related hospitalisation and mortality in Ethiopia, noting that measuring the effectiveness of such interventions is an area requiring further research.

In summary, this thesis has provided the most robust estimate of the extent and nature of the burden of ADR-related hospital admission and mortality in Ethiopian patients. Given the overburdening of the growing healthcare system with ADR-related hospitalisation and mortality, urgent work is required to:

- investigate the impacts of genetics, malnutrition, and chronic infectious and non-communicable diseases on the acquisition and outcomes of ADRs;
- develop robust methods for prevention of the occurrence of ADRs in the future; and
- evaluate the impact of ADR prevention strategies with the ultimate goal of preventing or reducing the risk of acquiring ADRs, improving patient outcomes and minimising ADR-related costs to the healthcare system.

Considering the significant problem of ADR-related admissions and mortality, and the lack of universally accepted standardised methods for assessing ADR causality, type, severity and preventability, there is a need to develop robust standardised methods in order to accurately estimate the worldwide epidemiology and financial costs of the problem to the health care system.

Table of contents

List of tables

List of figures

Chapter One

1. Introduction

"Our figures show approximately four and one half million hospital admissions annually due to the adverse reactions to drugs." Milton Silverman, M.D. (Professor of Pharmacology, University of California)

1.1 Background

The safe use of drugs is plausibly the single most important criteria that a regulatory authority within a given country has to ensure in order to protect the public health and the integrity of its healthcare system (1). In principle, the safety profile of a medicine is derived primarily from early phase adverse event data of randomised controlled trials (RCTs), which typically includes relatively small numbers of patients and normally has a short duration (2). RCTs are useful for detecting common adverse drug reactions (ADRs) that will occur with exposure to a drug and they may explain some serious ADRs (2). However, RCTs are less likely to be able to reveal rare ADRs, delayed ADRs that occur with prolonged use, delayed ADRs that occur after drug cessation, ADRs in special populations that are not routinely included in drug development, and ADRs from excipients (3). For these reasons, RCTs alone are not enough to establish the full safety profile of a drug, therefore, post-licensing safety data must be collected to further understand the adverse reactions associated with a drug and build up a true profile of its safety.

In 1961, serious adverse events, such as the development of limb defects called phocomelia, with thalidomide (4), and more recently, the abrupt worldwide withdrawal of rofecoxib due to its association with increased cardiovascular risk (5) have also widely highlighted the need for post-licensing studies or pharmacovigilance. Pharmacovigilance (PV) can be defined as the science and activities relating to the detection, assessment, understanding and prevention of

adverse effects or any other drug-related problems (6). The major aims of PV are early detection of unknown adverse reactions and interactions, detection of increases in frequency of known adverse reactions, identification of risk factors and possible mechanisms underlying adverse reactions, estimation of quantitative aspects of the benefit/risk analysis and dissemination of information needed to improve drug prescribing and regulation (6), thus, encouraging safer and more effective use of medicines.

Despite the implementation of PV systems over the past 50 years, neither the prevalence of ADRs nor their consequences have decreased (7-14) probably because the complexity of drug therapy has increased. Regardless of all the advantages of pharmacotherapy, ADRs are commonly recognised hazards of drug therapy that cause hospital admissions, morbidity, mortality and extra costs to the healthcare systems (11, 12, 15-20).

1.2 Definitions/terminologies

ADRs have been subject to several definitions. In 1972, the World Health Organisation (WHO) defined an ADR as “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function"(21). This definition is intended to include all doses used clinically but exclude deliberate overdose and has been used widely in ADR studies over the last 40 years (22, 23).

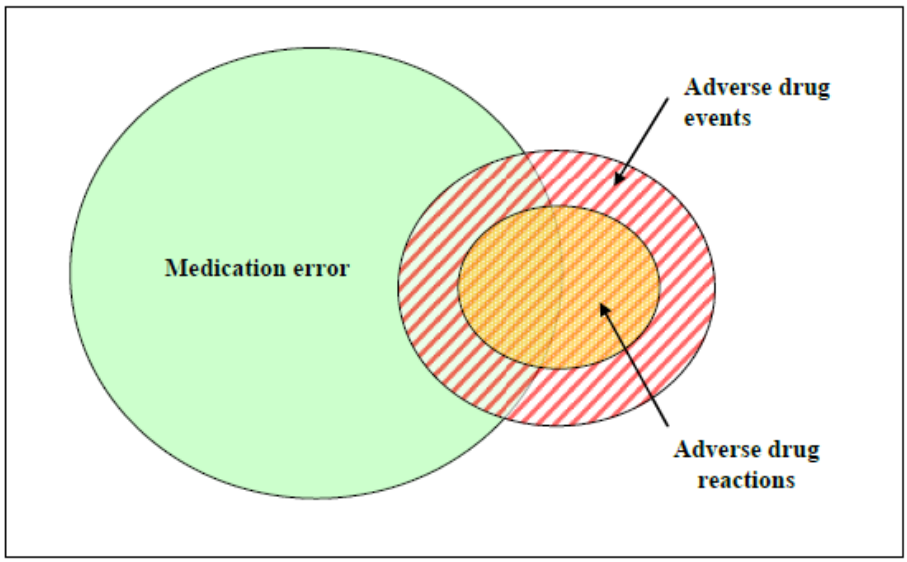
Edwards and Aronson (24) suggest the following as an alternative: “An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.” This definition includes

doses used clinically, however, it disregards ADRs requiring no intervention, and has been used in ADR epidemiological research (10).

Other definitions used in epidemiological studies which measure ADRs have a broader scope and examine adverse drug events (ADEs) as a whole. ADEs have been defined as "injury resulting from the medical intervention relating to the drug" (25). Therefore, all ADRs are ADEs but not all ADEs are ADRs. The terms are not used interchangeably as studies of ADEs can cover medication administration, prescription, and ordering errors. On the other hand, ADEs are not necessarily due to the drug itself. The term ADE is not particularly helpful to physicians, but it provides context for the more clinically useful term ADR. Additionally, ADRs occur despite appropriate prescribing and dosing, whereas ADEs may be associated with inappropriate use of the drug or other confounders that occur during drug therapy but are not necessarily caused by the pharmacology of the drug itself. Therefore, an ADR is an adverse event with a causal link to a drug. ADEs may also be caused by medication errors (MEs), which the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) (26) defines as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.”

According to Edwards and Aronson (24), “an adverse effect is defined as an adverse outcome that can be attributed to some action of a drug whereas an adverse event is an adverse outcome that occurs while a patient is taking a drug but is not or not necessarily attributable to it.” Therefore, the terms “adverse reaction” and “adverse effect” can be used interchangeably, except that an adverse effect is seen from the point of view of the drug, whereas an adverse reaction is seen from the point of view of the patient. However, the terms “adverse effect” and “adverse reaction” must be distinguished from the term “adverse event”.

Based on the above definitions, Nebeker et al. (25) illustrated the relationship between ADEs, ME and ADRs in 2004 as shown in Figure 1.1.



(Source: Adapted from (Nebeker et al., 2004)

Figure 1. 1 Model to describe types and relationships of risk from drug treatment (25)

Contrary to the above definitions, Morimoto et al. (27) defines an ADR as "a non-preventable ADE due to a medication where there is no error in the medication use process and includes an allergic reaction in a patient not previously known to be allergic to the medication or non-preventable reactions due to side effects or allergic reactions."

This introductory chapter will firstly examine the prevalence of ADR-related hospitalisation and associated burden and outcomes, the classification of ADRs and causality assessment methods and will then focus on reviewing the literature on common ADR presentations, implicated drugs and risk factors associated with hospitalisation, and review current knowledge regarding ADR prevention strategies. At the end of this chapter, the Ethiopian heathcare and ADR reporting systems, definitions and methods used in this study, and the rationale and main aims of the study are described.

1.3 Prevalence of ADR-related hospitalisation

Globally, the rates of ADR-related hospitalisation vary from 0.2% (28) to 54.5% (29). For instance, studies from developed countries reported a prevalence of 8.8% (of which 57.3% were preventable) in Ireland (30), 5.8% (of which 76.5% were preventable) in Italy (31), 7.5% (of which 66.7%) were preventable) in the United Kingdom (32) and 36.2% (of which 62.3% were preventable) in the United States (33).The few studies from developing countries have revealed a prevalence of 6.9% (of which 59.6% were preventable) in India (34), 6.3% (of which 53% were prevalent) in South Africa (23) and 10.7% (of which 85.7% were preventable) in Argentina (35). ADR-related mortality is also an important burden in medical care (36). The rates of fatal ADRs in patients presenting to hospital have been reported to range from 0.1% to 10% (20, 37) with comparable proportions in developed and developing countries.

1.4 Burden and outcomes of ADRs

1.4.1 ADR-related morbidity and severity

ADRs are an important healthcare problem, frequently associated with multiple detrimental outcomes. Some of these include hospital admissions, loss of confidence in treating doctors, increased costs of care, preclusion of the use of some drugs, unnecessary investigations, delay in treatment, and deaths (38). In addition, ADR-related morbidity decreases quality of life by causing worries and emotionally affecting the patient's belief in the use of medication for treatment, as well as causing physical morbidity in some cases (e.g. permanent incapacity or organ damage)(38). Moreover, ADRs cause life-threatening reactions, such as Stevens-Johnson Syndrome, prolongation of hospital stay, congenital anomaly or birth defects, significant disability or incapacity, and permanent organ damage (20, 39, 40). Although limited studies have focussed only on severe ADRs, the few available studies have reported that severe ADRs were important reasons for extension of the hospital stay in approximately 20% of

patients (41), and cause life-threatening effects and admission to intensive care unit in 1.8% to 18.6% of the cases (40, 42, 43).

ADR severity describes the extent to which the ADR influences the everyday life of the patients or it relates to the effect it has on the individual. Severity of ADR is distinct from seriousness. For instance, Edwards and Aronson (24) defined serious ADRs as "any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening." A severe reaction may not necessarily be serious. Severity of ADRs has been assessed using different scoring systems, such as the Karch et al. (44), Dormann et al. (45), and Hartwig et al. classifications (46). Karch et al. classify severity into minor, moderate, severe, and lethal. Dormann et al. devised an ADR severity score of mild, moderate or severe depending on the numerical score obtained when the algorithm is applied. It incorporates a quality of life assessment. A score of 1 to 4 indicates a mild, a score of 5 to 8 a moderate, and a score of >8 a severe ADR. The severity scale of Hartwig et al. has seven levels ranging from level 1 (where the ADR requires no change in the drug treatment), to level 7 (where the ADR is fatal). Levels 1 and 2 are less severe, levels 3 and 4 are moderate, and levels 5, 6 and 7 are classified as severe as indicated Table 1.1. The principles of ADR severity assessment by the Hartwig et al. method are based on length of stay, treatment required, and the patient's prognosis. This ADR severity assessment method is simple, easy to use, has clear definitions, and it has been widely applied in prospective studies of ADR-related hospitalisations (47, 48).

Different studies have revealed that 10.9% to 42.0% of the ADRs that led to admissions were classified as severe (9, 23, 47, 49-55) as indicated in Figure 1.2. For instance, out of 6.3% of ADR-related admissions, 14.1% were severe in a South African study (23). The majority of the severe ADRs required interventions, which ranged from stopping the causative agent(s) to

administration of specific antidotes. Therefore, the marked differences in the prevalence of severe ADRs in the studies discussed above were possibly due to the multiplicity of definitions of ADR severity and a lack of standardisation of the definitions across the studies.

Table 1. 1 Hartwig et al. classification of ADR severity

ADR severity scale	ADR severity level	Description of the level
Mild	Level 1	An ADR occurred but required no change in treatment with the suspected drug
	Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)
Moderate	Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed, and/or an antidote or other treatment was required. No increase in LOS
	Level 4	Any level 3 ADR which increases LOS by at least 1 day OR the ADR was the reason for the admission
Severe	Level 5	Any level 4 ADR which required intensive medical care
	Level 6	The adverse reaction caused permanent harm to the patient
	Level 7	The adverse reaction either directly or indirectly led to the death of the patient

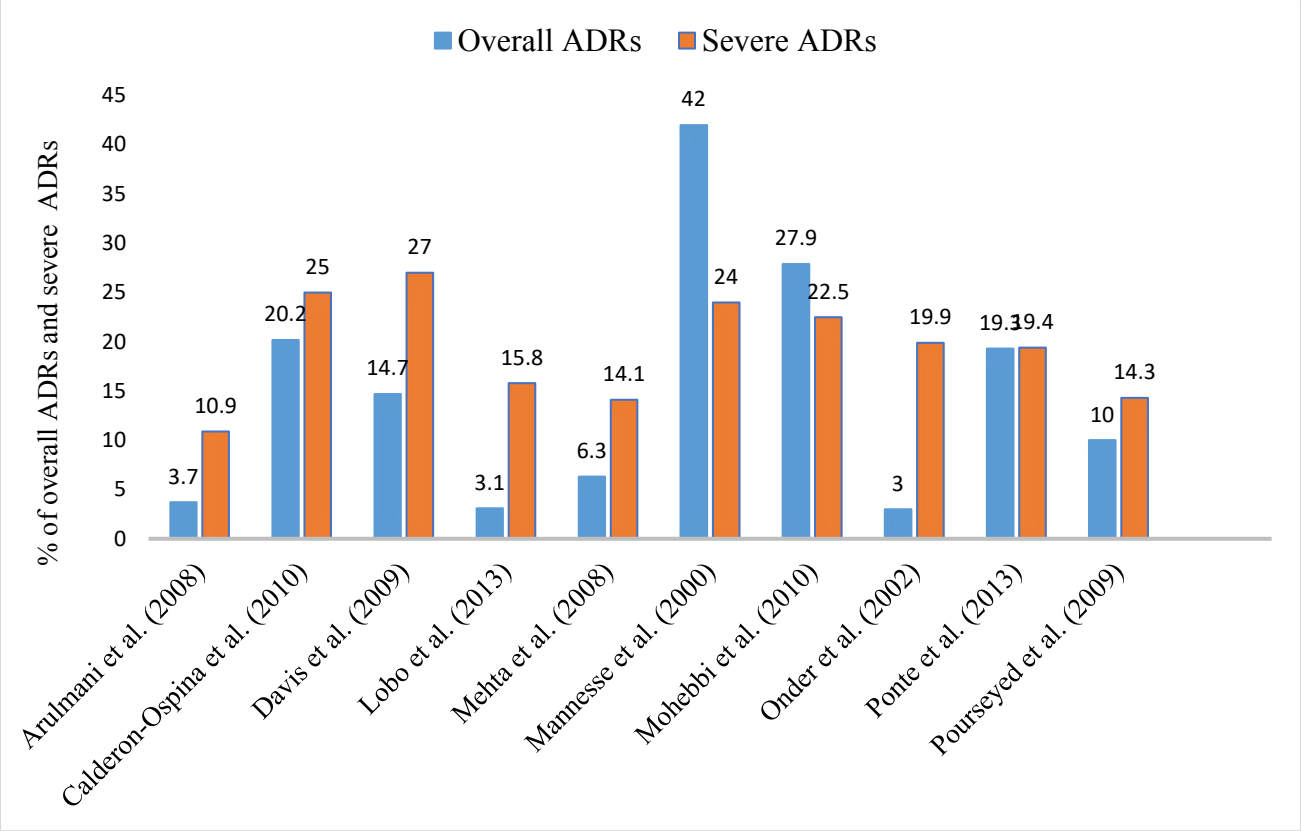


Figure 1. 2 Proportion of overall and severe ADRs in relevant studies (9, 23, 47, 49-51, 53-55).

1.4.2 ADR-related length of hospital stay

There is a relationship between the cost of care of a patient hospitalised for an ADR and the length of the hospital stay. A systematic review in the UK showed that ADRs led to prolongation of hospital stay and escalation of the hospital bed occupancy rate by approximately 15–20 in a 400-bed hospital (56). This systematic review of both prospective and retrospective studies was augmented by a prospective study by Pirmohamed et al. (10) illustrating an additional stay of 2.2 hospital days as a result of ADR. Another study in Australia (57) showed that there was an extraordinary escalation of age-related hospital stays due to ADRs; in 1981 it was 2.5 for every 1,000 person–years, increasing to almost 12.6 for every 1,000 person–years in 2002. Similarly, Rottenkolber et al. (58) from Germany revealed that

the average inpatient length of stay associated with ADR was 9.3 days, and the annual total health care cost was escalated due to ADRs. Mehta et al. (23) from South Africa reported that the median length of hospital stay in patients with ADRs was longer than in those without ADRs (8 (5-12) days vs. 6 (4-9) days) constituting 5.8% of bed occupancy.

1.4.3 ADR-related mortality

ADR-related mortality is a significant public health problem (59). According to a systematic review of 39 studies between 1970 and 2002 (60), ADR was recorded as the fourth leading cause of death in the US after heart disease, cancer and strokes. In this review, it was found that 106,000 people died because of ADRs and more than 2 million suffered serious side effects with a trend showing increasing death and injury from ADRs. In Australia, Hodgkinson reported that death occurred in 0.7% of ADR cases in 2004 (61). Pirmohamed et al. (10) from the UK revealed that over 2% of patients admitted with an ADR died between November 2001 and August 2002, suggesting that ADRs may be responsible for the death of 0.15% of all patients admitted. A retrospective study conducted by Wester et al. (40) in a Swedish population found that fatal ADRs accounted for approximately 3% of all deaths in the general population between January 2001 to December 2001, where fatal ADRs were estimated to be the seventh most common cause of death. A 20-year survey that was concducted between 1974 and 1993 in three Swiss teaching hospitals reported an ADR-related mortality rate of 0.054% of admissions (62). A study in a Finnish University Hospital in 2000 revealed that deaths in 0.05% of hospital admissions (5% of in-hospital deaths) were attributed to ADRs (63).

Although there are scanty data on the mortality rate of ADRs in low and middle-income countries, the few available studies reported a mortality rate that ranged from 0.24% (64) to 10% (37) . ADR-related mortality rates of 0.24% of all admissions in a study conducted in a 6 month period in 2011 (64) and 2.5% from 665 adult patients admitted to medical wards in a 3

month period in 2005 (23) were reported from India and South Africa, respectively. Another study which was conducted in South Africa between April and Septmeber 2013 (65) reported that ADRs contributed to the death of 2.9% of medical admissions; the overall mortality rate in these study wards was 18 per 100 admissions. Prevalence of ADR-related deaths as a proportion of study setting admissions in some studies are presented in Figure 1.3.

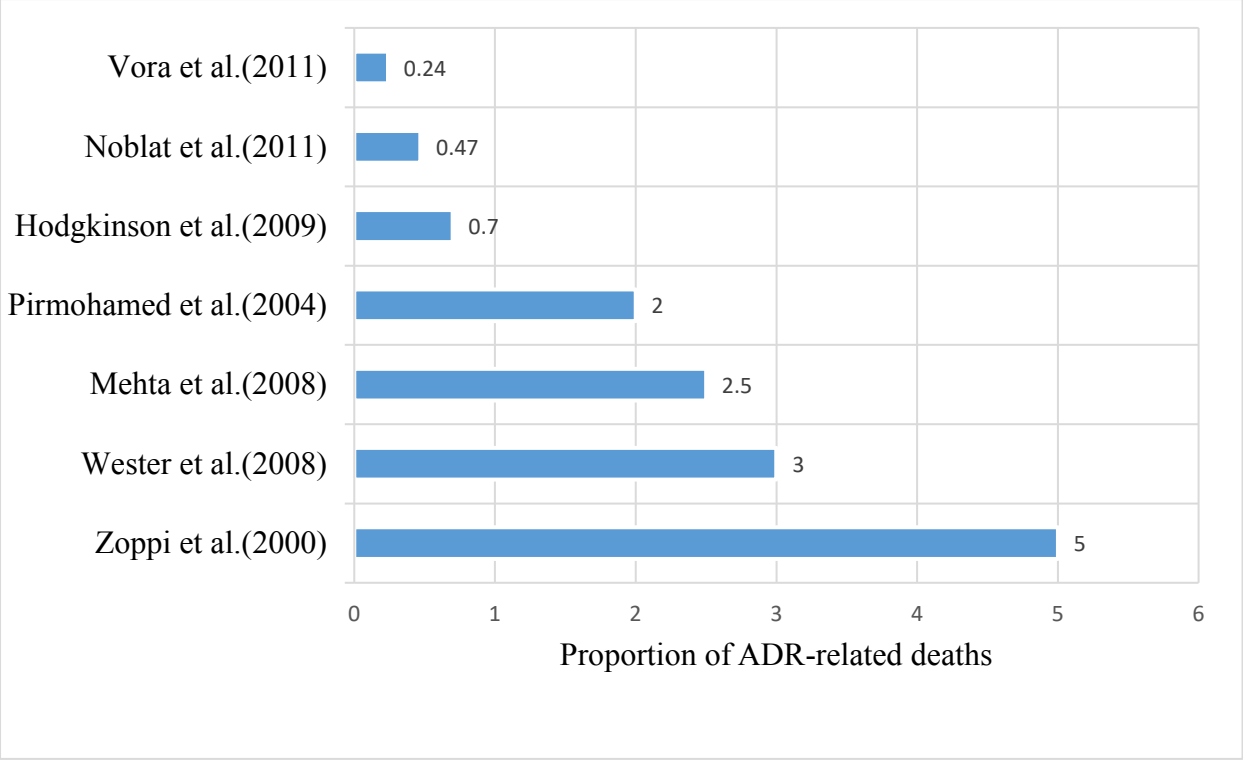


Figure 1. 3 Prevalence of ADR-related deaths in relevant studies (10, 23, 40, 61, 62, 64-66).

1.4.4 ADR-related economic burden

The increase in costs due to ADRs are related to the increased length of hospital stay and additional medical care provided to the patients. For instance, Classen et al. estimated that hospital admissions due to ADRs increased the cost of patient care by USD 2,262 per patient (67). According to Wu et al.'s (68) estimation in 2008, the cost of ADR-related visits to emergency departments was CAD 333 per visit and CAD 7,528 per hospitalisation for a total annual cost of CAD 13.6 million in Ontario, or an estimated CAD 35.7 million in Canada.

Another burden of ADRs is attributable to prescribing new medication to treat the ADR, which increases the drug use in those patients (69). Litigation or malpractice-related costs are also burden of ADR that is frequently overlooked. For instance, Rothschild et al. (70) reported that ADRs represented 6.3% of malpractice claims by a New England malpractice insurance company, of which, 46% of the events were life-threatening or fatal and 73% of them were judged to be preventable. Those preventable drug events were estimated to cost USD 50.7 million in 2001, which does not include additional costs such as plaintiffs' legal expenses. Litigation against the healthcare provider can also be professionally and emotionally distressing, and long-term physician-patient relationships can also be affected due to loss of trust (71). In general, preventable ADRs should be the primary focus for implementing strategies that can help reduce the burden of ADRs.

1.5 Classification of ADRs

There are many ways of classifying ADRs. Although there is no consensus in the mechanisms of ADRs, it can be broadly classified on the basis of either the presence or absence of immune mediation (72). The terms "drug allergy", "drug hypersensitivity", and "drug reaction" are used interchangeably, however, drug reaction embraces all adverse events related to drug administration, regardless of aetiology. Drug hypersensitivity means an immune-mediated response to a drug agent in a sensitised patient whereas drug allergy is restricted specifically to a reaction mediated by IgE (73). The majority (75% to 80%) of ADRs are pharmacologically predictable and non-immunologic whereas the remaining 20% to 25% are unpredictable and immune-mediated (74). Specifically, IgE-mediated drug allergies account for 5% to 10% of all drug reactions and constitute true drug hypersensitivity (72, 73).

Rawlins and Thompson (75) first formally classified the mechanisms of ADRs in 1977 as type A and type B. Type A ADRs are dose dependent and predictable from the known pharmacology

of the drug. Type A ADRs commonly result from an exaggeration (augmentation) of a drug's normal pharmacological action when given in the usual therapeutic dose. The severity of type A reactions ranges from minor to life-threatening effects. Because of their characteristics, the majority of type A ADRs are identified prior to product authorisation and are consequently listed in product labelling. Examples include hypoglycaemia with antidiabetic agents, bleeding with warfarin, and hypotension with beta-blockers. On the contrary, type B ADRs are not dose dependent, hence, are unpredictable. Perhaps partially because of their non-dose dependence and unpredictability, they are considered more serious than type A ADRs and appear to be associated with a higher rate of mortality (24). Due to unsubstantiated relationship to dose, type B ADRs can occur at any time after the drug has been started; emerging at any time during the course of therapy and sometimes after treatment has stopped (24). In addition, because of their tendency to be severe, re-challenge is dangerous. Therefore, the drug is usually discontinued if a patient experiences a type B ADR. Many type B ADRs are only revealed post-authorisation when a greater number of patients are exposed to the drug. One example includes anaphylactic reactions to antibiotics. According to previous studies (32, 47, 51, 55, 76, 77), 75% to 91% of ADRs have been classified as type A reactions based on Rawlins and Thompson's classification method. This classification is simple; it helps drug regulatory bodies because pre-licensing studies can reveal type A reactions (78), and it predicts that dose titration will increase the risk of some reactions. This classification system is the most widely accepted and recognised in the literature.

According to the above ADR classification, it is sometimes impossible to assign a reaction to one type. Therefore, the above ADR classification has gradually been extended to alphabetically labelled types, including type C (dose and time dependent (chronic) reactions), type D (delayed reactions), type E (withdrawal reactions), and type F (failure of therapy) (79).

This classification has mitigated some of the difficulties of the Rawlins and Thompson classification but has introduced others.

Aronson et al. (80) highlighted the limitations of the above classifications, and considered other parameters to classify the ADRs. These are time course, appearance and severity of the reaction, and the susceptibility of the individual, which are expressed as dose-relatedness, timing, and patient susceptibility (DoTS). Dose-related ADRs occur at supratherapeutic doses (toxic effects), standard therapeutic doses (collateral effects) and sub-therapeutic doses in susceptible patients (hyper-susceptibility reactions). With regard to timing, ADRs can be time dependent (the ADR depends on both the concentration of the drug at the site of action and the time course of its appearance there) and time independent (the ADR occurs at any time during treatment, independent of the duration of the course). According to this classification, the time dependent ADR can be sub classified into six subtypes - rapid, first dose, early, intermediate, late, and delayed reactions (80).

1.6 ADR causality assessment

Identifying the cause of a suspected ADR is a complex process because many patients take more than one drug that can often make detection of the causative agent problematic. Alternatively, the suspected ADR may in fact be a manifestation of other underlying disease states (81). Therefore, an important step in recognising an ADR and assessing causality is to obtain an accurate patient drug list through review of medical records and interview with patients or family members about medication usage. Then, it is crucial to establish a causal relationship between the suspected drug and the ADR in order to clearly indicate the burden of ADRs.

Many ADR causality assessment methods have been proposed to judge the relationship between a drug and an adverse reaction in a given patient, ranging from expert judgment to comprehensive algorithms. However, there is no universally accepted method for assessing causality of ADRs as a result of problems of reproducibility and validity (82). There are principally three types of method for causality assessment which are practical for regular use (82). These are: unstructured assessment by an assessor or a panel of assessors (global introspection), semi-structured assessment using pre-set guidelines, and standardised assessment using decision tables or algorithms. A fourth method, using the application of Bayesian statistics (the Bayesian Adverse Reaction Diagnostic Instrument: BARDI), has also been devised but its complexity has limited its use.

The global introspection of ADR causality assessment is based on consensus agreement/personal judgement of each ADR report by the expert/investigator, following careful review of the case notes/medical records, laboratory parameters and application of clinical opinion. Because of its subjectivity, lower levels of certainty, and lack of transparency, it has been designated as an unsuitable method for assessing ADRs (83).

Semi-structured ADR assessments, such as the World Health Organisation Uppsala Monitoring Centre (WHO-UMC) causality assessment method (84), provide guidelines for assigning a causality term, i.e. 'definite', 'probable', 'possible' and 'unlikely' ADR, without providing specific rules as to how the causality assessment should be carried out. The WHO-UMC causality assessment method (84) was developed in consultation with the National Centres participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. This causality assessment method has advantages over the unstructured method in that the guidelines for classifying the causality of an ADR are clear, which allows other investigators to understand how a conclusion was drawn. The various

causality categories and the assessment criteria of the WHO-UMC system are summarised in Table 1.2.

Table 1. 2 WHO-UMC ADR causality categories

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake • that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Source: Adapted from WHO-UMC ADR causality assessment **(84)**.
*All points should be reasonably complied with

Unstructured and sometimes semi-structured ADR causality assessment methods have a limited role in observational studies due to their subjectivity in assessing the temporal

relationship between the suspected drug and the ADR. In order to solve these problems, many standardised algorithms, such as the Irey (85), Karch (86), Kramer (87) and Naranjo (88) algorithms, have been developed to assess the causality of ADRs. The first structured ADR causality algorithm that depends mainly on time-relationship and pathological evidences of the suspected drug and event was developed in 1976 by Irey (85). Following this, Karch et al. (86) published a three-decision-table algorithm that requires evidence of a previously documented ADR having been associated with the suspected drug in question. This algorithm helps the user to assess potential drug reactions, the certainty of the link between the drug and event and the underlying cause of the detected adverse event. Then, Kramer (87) expanded the work of Karch et al. to a six-decision-table algorithm with a new scoring system through assessing previous general experience with the drug, alternative aetiologic candidates, timing of events, drug levels and evidence of overdose, dechallenge and rechallenge.

Another algorithm, published in 1981, developed by Naranjo and co-workers (88) from the University of Toronto is often referred to as the Naranjo Probability Scale. Although it was not in use in routine clinical practice at that time, it helped standardise assessment of causality for all ADRs as it was initially designed for use in controlled trials and registration studies of new medications. Since then researchers have widely used it in observational studies because of its simplicity to apply and its objective measurement. It consists of 10 questions that are answered as either Yes, No, or "Do not know". Different point values (-1, 0, +1 or +2) are assigned to each answer for the 10 questions. The values assigned to each question answered are totalled, and the final score corresponds to causality categories of 'definite', 'probable', 'possible' or 'doubtful'. Total scores range from -4 to +13; the reaction is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less as illustrated in Table 1.3. The Naranjo ADR Probability Scale is quick to complete and has moderate reliability (89, 90) when compared to other more comprehensive and detailed methods.

Table 1. 3 Naranjo ADR assessment algorithm/scale (88)

Question	Yes	No	Do Not Know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
*4. Did the adverse event reappear when the drug was readministered?	+2	-1	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

* This question evaluates the response to rechallenge or re-exposure. An answer of "Yes" (+2) indicates that the medication was stopped, the ADR resolved or improved, and there was an unequivocal reappearance or worsening of the reaction when the medicine was restarted in a similar dose and by the same route. The Naranjo scale also allows for a "Yes" if the causal association is well known and rechallenge cannot be done for clinical or ethical reasons.

The last type of ADR causality assessment is the BARDI method that calculates the posterior probability, a ratio between two probabilities both of which are conditional on the same background and case information, in favour of a specific drug cause based on background (e.g., epidemiologic) and case information (e.g. time of onset) (91). These approaches use specific findings in a case to transform the prior estimate of probability into a posterior estimate of probability of drug causation. The prior probability is calculated from epidemiological

information and the posterior probability combines this background information with the evidence in the individual case to come up with an estimate of causation. The BARDI is advantageous in that it discriminates between drug and non-drug-induced ADRs while its complexity limits its use in routine practice. The risk of acquiring an ADR differs among an exposed population. In some cases, the risk of an ADR will be present in susceptible patients and absent in others.

1.7 Drugs commonly implicated in ADR-related hospitalisations

Based on the different ADR causality assessment methods, drugs commonly implicated in ADR-related hospitalisations have been identified and reported in different studies. Certain drugs are associated with an increased risk of adverse reactions or interactions due mainly to a low therapeutic ratio (i.e. the difference between a therapeutic and toxic dose is low) (92). These include oral anticoagulants, oral hypoglycaemic agents, some antihypertensives, many cytotoxic agents, anti-convulsants, corticosteroids, some antimicrobials, and nonsteroidal anti-inflammatory drugs (NSAIDs). According to the reports of different studies, drug classes commonly implicated in ADR-related hospitalisations included antithrombotics (16, 35, 93-97), cardiovascular agents (17, 20, 30, 94, 98, 99), NSAIDs (10, 16, 23, 35, 39, 93, 95, 98) and antimicrobials (33, 42, 66, 100) as summarised in Figure 1.4 below. In addition, drugs commonly implicated in causing severe ADRs are listed in Table 1.4. Antimicrobials, mainly anti-tuberculosis and antiretroviral therapies, were more commonly implicated in ADR-related hospitalisations in developing countries than developed countries (23, 34, 66, 101).

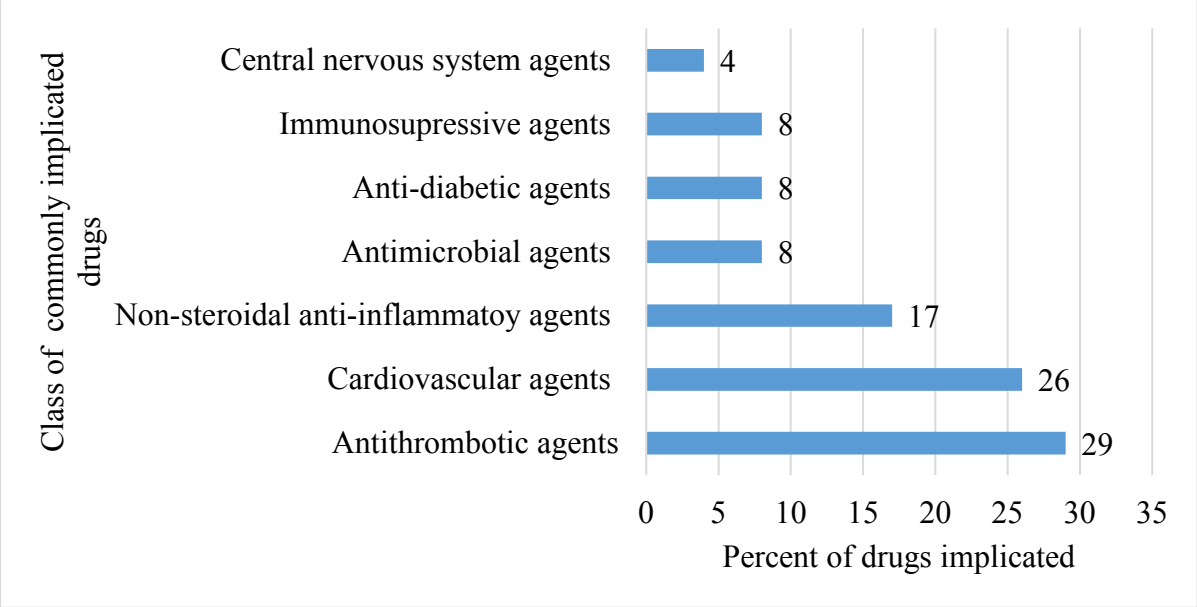


Figure 1. 4 Drug classes commonly implicated in causing ADRs as per reports of relevant studies (9-11, 15, 16, 20, 23, 30, 32, 33, 35-37, 39, 42, 55, 59, 66, 76, 93, 94, 96-98, 100, 102-108).

Table 1. 4 Drugs most frequently involved in serious ADRs

Angiotensin-converting enzyme inhibitors (enalapril, lisinopril) (109)
Anticonvulsants (phenobarbital, phenytoin/fosphenytoin) (110, 111)
Antimicrobials (amoxicillin, ciprofloxacin, efavirenz, gentamicin, isoniazid, nevirapine, tenofovir, pyrazinamide) (23, 42, 65, 66, 96, 101, 112-114)
Antipsychotics (haloperidol, quetiapine, zuclopenthixol) (115-117)
Antithrombotics and coagulation inhibitors (acetylsalicylic acid, clopidogrel, enoxaparin, and warfarin) (110, 114, 116, 118)
Benzodiazepines (midazolam, triazolam) (119-121)
Beta-blockers (metoprolol) (10, 110, 122)
Calcium channel blockers (nifedipine) (111, 123)
Corticosteroids (prednisolone) (110, 111)
Cytostatics (carboplatin, daunorubicin, etoposide, 5-fluoruracil, methotrexate) (110, 123)
Diuretics (furosemide) (110, 117, 124)
Insulin (125-128)
NSAIDs (diclofenac, ibuprofen, indomethacin) (10, 32, 97, 129, 130)

1.8 ADRs commonly associated with hospitalisations

ADRs are commonly reported in both developed and developing countries although there is considerable variation in disease distribution (9, 14, 23, 100), population characteristics (9, 14, 23, 100), healthcare systems (104) and complexity of diseases and medications prescribed (9, 14, 94). These included, but were not limited to, gastro-intestinal (GI) bleeding (20, 97, 99, 100, 105), cardiovascular disorders (16, 23, 30, 32, 37, 93, 94), electrolyte and metabolic disturbances (9, 16, 23, 58, 94), neuropsychiatric and central nervous system disorders (28, 131) and cytotoxicity (110, 123). In contrary to developed countries, studies from developing countries have revealed that drug-induced hepatotoxicity (DIH) (mainly due to anti-TB and ART agents) (23, 34) followed by drug-induced acute kidney injury (mainly due to ART agents) (101) were the major reasons for hospital admissions, reflecting the high burden of tuberculosis and HIV/AIDS in these settings.

DIH is an important cause of hospitalisation (132), responsible for over 50% of acute liver failure (ALF) (133, 134) and remains a top reason for drug withdrawal from the market creating cost and medication availability ramifications (133, 135). DIH has a profound impact on healthcare by causing substantial morbidity and mortality, and healthcare expenditures (136). Drugs commonly implicated in DIH were antimicrobials, such as anti-tuberculosis drugs (137, 138), and cytotoxic agents (139, 140). The patterns of DIH as hepatocellular, cholestatic, and a mixed-type, and may vary for the same drug. Studies have reported that the cholestatic pattern of DIH accounts for 20% to 40% of DIH, the hepatocellular pattern accounts for 40% to 78%, and the mixed pattern accounts for 12% to 20% (141, 142).

Drug-induced acute kidney injury (AKI) is another common ADR characterised by elevations in blood urea nitrogen (BUN) and serum creatinine (SCr) levels. It results in electrolyte and acid-base abnormalities and retention of nitrogenous waste products, such as urea and

creatinine (143). Patients with drug-induced AKI are often asymptomatic, but when they are symptomatic, they present with anorexia, fatigue, mental status changes, nausea, vomiting, pruritus, seizures if BUN levels are extremely high, and shortness of breath if volume overload is present (144). However, alterations in urine volume may be the only symptom that patients notice. Populations most at risk include the elderly, those with underlying renal insufficiency, cirrhosis, nephrotic syndrome, or congestive heart failure (145). Drug-induced AKI is a common medical problem requiring hospitalisation and the incidence of drug-induced AKI may be as high as 60% (146). Drugs frequently implicated in drug-induced AKI were diuretics (e.g. furosemide), ACE-inhibitors (e.g. enalapril), antiretroviral therapy (e.g. tenofovir) and NSAIDS (e.g. diclofenac) (23, 65, 101, 147-149).

1.9 Risk factors for ADRs

Despite the concerns that ADR-related hospitalisation, morbidity and mortality represent an important medical problem in the healthcare system, predictive factors for ADR are still poorly understood. One important strategy for preventing ADR-related hospitalisation and mortality is to identify the patients who are at risk of an ADR and to target additional resources toward these groups. Although multiple risk factors have been reported, there is no uniformity in reports due to the differences in the demographics of the study participants, healthcare systems, and disease distributions. Many studies have identified several risk factors contributing to ADR-related hospitalisations; these are discussed in more detail below. Figure 1.5 shows the relationship between different risk factors and ADR-related hospitalisation based on previously published study findings.

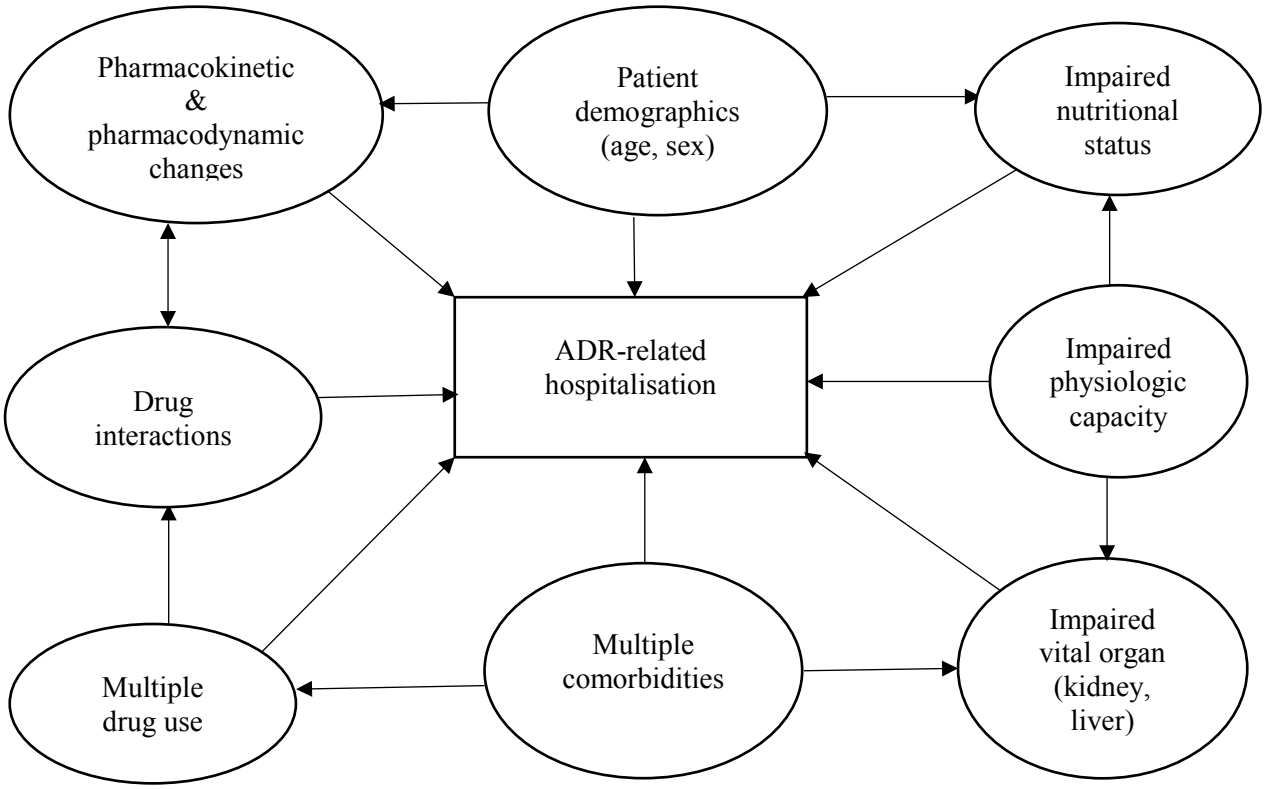


Figure 1. 5 The relationship between factors contributing to ADR-related hospitalisations

1.9.1 Age

Many studies (9, 30, 34, 55, 58, 96, 97, 137, 150-165) report that advanced age has been found to be a risk factor for ADR-related admission, irrespective of the socioeconomic status of the patients. This was mainly because of increased fragility, medical complexity, disease burden and physiological changes with increased age. In addition, as age advances, there is impairment of the kidneys and liver that lead to decreased excretion of drugs into the urine and biotransformation of many drugs, respectively (102). The amount of water in the body decreases and the amount of fat tissue relative to water increases, potentially leading to higher concentrations of drugs that dissolve in water and in fat. On the contrary, Mjorndal et al. (166) and Hellden et al. (167) reported that age itself had no effect on ADR-related hospitalisations that could alternatively be explained by appropriate adjustment of pharmacotherapy in response to impaired renal function.

1.9.2 Sex

Compared to males, females have lower body weight and organ size, more body fat, different gastric motility and a lower glomerular filtration rate (168), which results in variable drug pharmacokinetics and pharmacodynamics. Studies (14, 169, 170) have reported that being female was associated with increased risk of ADR-related hospitalisation in comparison to males taking similar medications. For instance, a study conducted by Rodenburg et al. (171) has reported that females showed most marked differences in incidence of ADR-related hospital admissions for different cardiovascular drug groups, such as cardiotonic glycosides, high-ceiling diuretics and coronary vasodilators. The possible reasons reported were multifactorial. Hepatic enzyme CYP3A4 is more active in females than males, which leads to different effects on drug metabolism (172, 173). Female specific concerns such as pregnancy, menopause and menstruation may have profound effects (174). Ensom et al. (175) reported that after the age of 45 years, when all sex-specific conditions were controlled, females had approximately 10–20% more physician visits and subsequently used more medications than males.

1.9.3 Comorbidity and polypharmacy

Multiple diseases make patients more vulnerable to ADRs due to the use of many drugs that increased opportunity for drug-drug interactions (9, 176). Increasing numbers of both co-morbidities and medications lead to increased medical complexity, which has been associated with an increased risk of ADR-related hospitalisation, especially with advancing age (9, 176). Furthermore, irrespective of the age of the patients, the number of medications taken has been a consistently reported risk factor for ADR-related admissions (14, 17). The risk of ADR severity also increases as the number of medications increases . Moreover, multiple diseases are a very important factor which causes drug-disease interactions and as a result ADRs (168).

Drugs that are helpful in one disease are harmful in another. For instance, some beta-blockers used for treatment of ischaemic heart diseases or high blood pressure can worsen respiratory symptoms and make it hard for people with diabetes by masking the signs and symptoms of low blood sugar (168).

1.9.4 Hepatic and renal failure

The pharmacokinetics of drugs can be affected in patients with impaired hepatic function since the liver is the main organ for metabolism and detoxification of endogenous and exogenous substances (177). In patients with abnormal intestinal permeability, the bioavailability of some drugs, such as drugs with a high hepatic extraction ratio is increased (178), as the absorption process may be altered due to porto-systemic shunting (179, 180). In patients with hepatic impairment, the free concentration of highly protein-bound drugs is increased due to hypoalbuminaemia (180). Hepatic impairment is also associated with a reduction or impairment of drug-metabolising enzymes that may cause reduced metabolism. These changes often result in an elevated drug exposure, and possibly ADRs (180, 181). For example, about 30% of patients with cirrhosis suffer ADRs and it is estimated that nearly 80% of these ADRs could be prevented (182).

Impaired renal function can have marked effects on the pharmacokinetics of many drugs because of changes in glomerular filtration, tubular secretion, reabsorption or metabolism (183). These may cause accumulation of the medicines or their metabolites, which may result in toxicity. The toxicity may be severe, especially if the medicine has a narrow therapeutic index (184). There is an increased risk of ADRs due to the use of contraindicated drugs and inappropriate doses (185). Studies have reported that patients with impaired renal function were more likely to be hospitalised with ADRs than patients with normal renal function (186,

187). The risk of acute kidney injury and subsequent drug-related adverse effects was higher in patients with a lower body mass index (162).

1.9.5 Alcohol consumption

Alcohol affects the metabolism of many drugs and promotes the occurrence of ADRs through both pharmacokinetic and pharmacodynamic changes (188). Taking alcohol with some drugs can cause many ADRs like nausea, vomiting, headaches, drowsiness, fainting, loss of coordination, and hypotension (189), which sometimes lead to acute hospitalisations. If alcohol is concomitantly taken with NSAIDS, it may cause internal bleeding due to enhancing severe ulceration in patients with peptic ulcer or ex-peptic ulcer or gastritis (190). Onder et al. (9) reported that moderate alcohol consumption was associated with a 24% increased risk of ADR-related hospital admission. This effect seemed more evident in women than men, while it was similar across different age groups. Considering the most common ADRs, moderate alcohol users presented a significantly higher risk of drug-related and metabolic/endocrine complications (191). Przybylski et al. (192) from Poland reported that alcohol abuse was independently associated with ADR-related hospitalisation among TB patients and lead to unsuccessful TB treatment of 10.5% of the patients.

1.9.6 Malnutrition

Malnutrition (based on BMI, protein-energy or micronutrient deficiencies) is one of the major public health problems world-wide, especially in most developing countries (193). There are multiple aggravating factors in developing countries, such as the high burden of TB and HIV infection, which adversely affect the nutritional status of patients (193-195). Malnutrition leads to adverse drug outcomes as the pathophysiological changes encountered in nutrient deficiencies interfere with pharmacokinetic and pharmacodynamic processes in the body (196). Malnutrition can also alter plasma and tissue protein quantitatively (197). Therefore, the

plasma protein binding capacity for commonly used drugs, such as anti-inflammatory and anti-TB drugs can be decreased, resulting in an increased free fraction of the drug and hence ADRs. In addition, patients with hepatic and renal impairment are exceptionally vulnerable to developing malnutrition because of the key role played by the liver and kidney in regulating the nutritional state and energy balance. When these are adversely affected, the risk of ADR increases (198).

1.9.7 HIV/AIDS and using antiretroviral therapy

Immunosuppression with HIV and opportunistic infections are a known risk factor for ADR-related hospitalisation (199). Mehta et al. (23) reported that patients' HIV positive status tended to increase the risk of experiencing ADRs and mortality compared to those who were HIV negative or whose HIV status was unknown. HIV-infected patients taking antiretroviral therapy (ART) were also more likely to be admitted with an ADR than those not taking ART (23). Dimie et al. (199) reported that AIDS-defining illnesses due to direct ART-related complications in general and zidovudine-induced severe anaemia requiring blood transfusions in particular were the most common reasons for hospital admissions. Severe anaemia increased the risk of mortality six-fold. Similarly, Henry et al. (200) from Cameroon reported that zidovudine-related severe anaemia was one of the common reasons for hospital admissions.

1.10 Preventing ADRs

The logical approach for improving patient care and reducing the incidence of ADR-related hospitalisation is to focus on preventable or avoidable types of ADRs. Measuring preventability is important to classify ADRs as preventable or not preventable, but the ultimate aim remains to characterise those preventable ADRs, highlighting the clinical situations and drug classes related to the risk. To date, there is no gold standard method for assessing

preventability of ADRs, however, the majority of the studies conducted in this field have used the modified Schumock and Thornton (201) criteria followed by Hallas' avoidability assessment criteria (202).

Hallas et al. suggested a quick outline to aid in assessor rating of preventability of ADRs (202). Hallas defines three categories - unavoidable, possibly avoidable and definitely avoidable. Unavoidable means the ADR could not have been avoided by any reasonable means. Possibly avoidable means the ADR could have been avoided by an effort exceeding the obligatory demands of present day knowledge of good medical practice. Definitely avoidable means the ADR was due to drug treatment procedures inconsistent with present day knowledge of good medical practice.

Studies show conflicting evidence on which instrument have the highest reliability for assessing ADR preventability (203, 204). Reliability was not reported in most studies and when reported, it varied markedly across studies. It was demonstrated that intra- and inter-rater reliabilities of the preventability judgements of ADRs were poorer when using implicit instruments compared to an explicit algorithm (205), perhaps due to the larger impact of the individual reviewers' clinical judgement in implicit instruments. Therefore, studies summarised in Figure 1.6 show wide variations in the rates of preventable ADRs reported, ranging from 20.1% to 83.3% (11, 30, 32, 34, 41, 47, 50, 55, 58, 95, 152, 206).

Table 1. 5 Schumock and Thornton criteria for assessing ADR preventability (201).

Preventability scale	Description of each scale
a) Definitely Preventable	1. Was there a history of allergy or previous reactions to the drug? □ Yes □ No 2. Was the drug involved inappropriate for the patient's clinical condition? □ Yes □ No 3. Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state? □ Yes □ No 4. Was a toxic serum drug concentration (or laboratory-monitoring test) documented? □ Yes □ No 5. Was there a known treatment for the adverse drug reaction? □ Yes □ No
b) Probably Preventable	1. Was required therapeutic drug monitoring or other necessary laboratory tests not performed? □ Yes □ No 2. Was a drug interaction involved in the ADR? □ Yes □ No 3. Was poor compliance involved in the ADR? □ Yes □ No 4. Were preventative measures not prescribed or administered to the patient? □ Yes □ No
c) Not preventable	If all above criteria not fulfilled

Answering "yes" to one or more of the questions in section "a" of the modified Schumock and Thornton criteria implies that an ADR is definitely preventable. If the answers are all negative to section "a", then one proceeds to section "b". Answering "yes" to one or more of the questions in section "b" implies that an ADR is probably preventable and if the answers are all negative to section "b", then one proceeds to section "c". In section "c", the ADR is not preventable as described in Table 1.5 above.

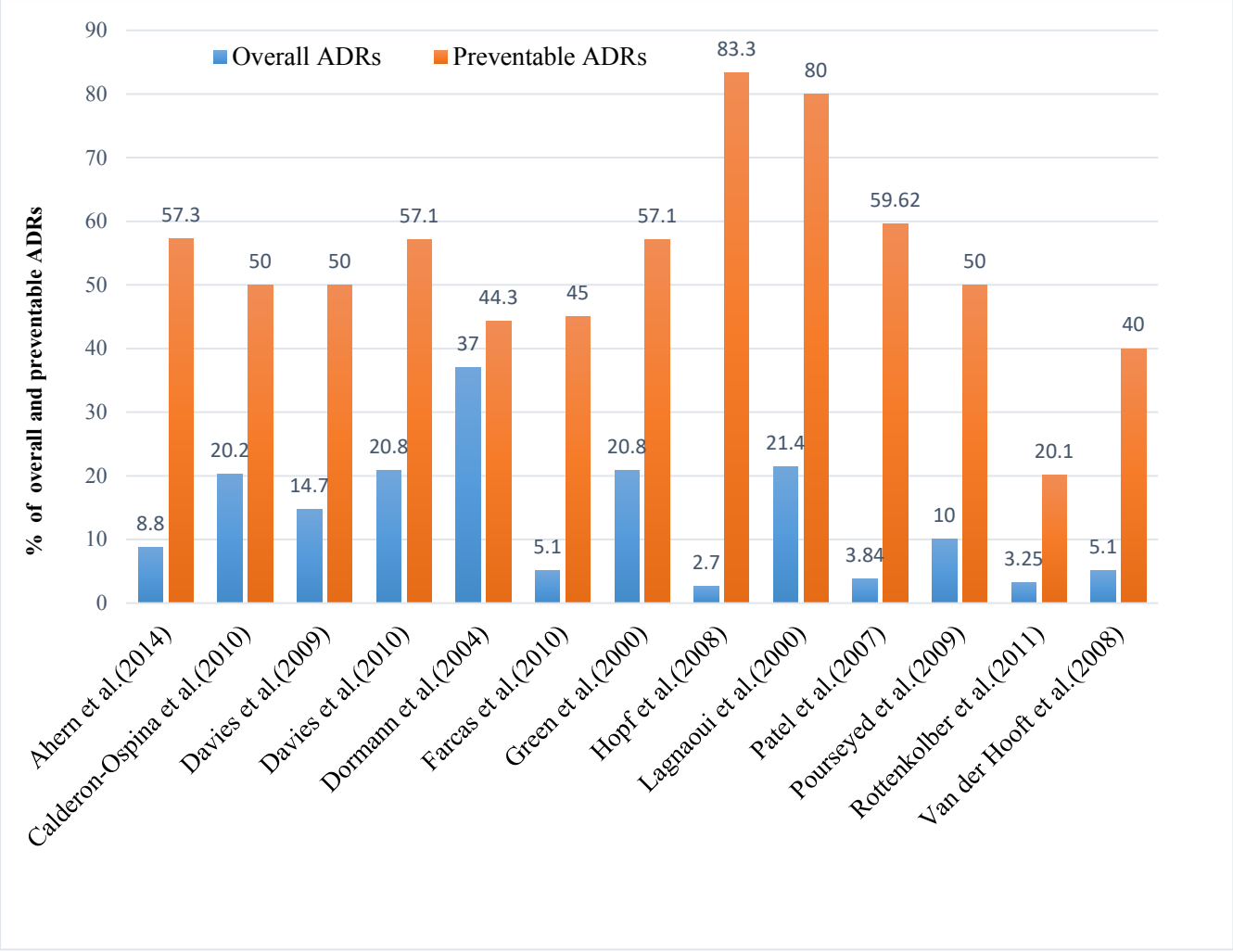


Figure 1. 6 Proportion of overall and preventable ADRs of relevant studies (11, 30, 32, 34, 41, 47, 50, 55, 58, 95, 152, 206).

1.11 Strategies for preventing ADRs

Strategies for preventing ADR-related hospitalisations focus on either the process of care or highlighting patients at risk of ADRs or both, so that appropriate interventions can be tailored to prevent the occurrence of an ADR (14, 207-209). For successful prevention of ADR-related admission, it is advisable to use a combination of both strategies as the healthcare environment and patients' clinical characteristics are complex in nature. ADR preventative strategies focusing on processes of care includes: utilisation of a computerised system, pharmacy-led

interventions, strengthening pharmacovigilance and ADR reporting systems, use of clinical tools, monitoring ongoing drug therapy, and preventing drug interactions.

The second ADR prevention strategy involves the identification of risks or developing risk prediction models to identify patients at risk of ADR. A primary effort to develop a risk prediction model was ensued by Elnicki and Schmitt in 1980 using ADE as an outcome (210). Approximately a decade later, Bates et al. (211) identified two independent variables, patients admitted to ICU and those with longer length of stay, predictive of ADE in a cohort of 4108 admissions. Based on their finding, Bates et al. concluded that preventive strategy based on patient risk identification is less effective and recommended system-based approach as an alternative. In 2006, Johnston and colleagues (212) identified specific patients and clinical characteristics related to increased risk of experiencing adverse events (including ADRs), using a study population of 60,206. They found that age group (<1 year & ≥60 year), diagnosis, admission sources, types of insurance, and the use of specific medications or medication classes were associated with increased risk of adverse events (212). Another study by Zopf et al. (14) identified five independent predictors of ADRs. These were increased temperature, low thrombocyte levels, low erythrocyte levels, multiple drug use and female sex, with an AUROC of 80.0%, sensitivity of 64.0%, and specificity of 86.0%. More recently, Parameswaran et al. (213) identified five independent predictors of ADR-related hospitalisations in elderly patients with an AUROC of 70%. According to this study, independent variables predictive of ADR-related admissions in the elderly were drug changes in the preceding 3 months, presence of renal failure and dementia, use of antihypertensives and anticholinergics. Many studies have identified several strategies for preventing ADR-related hospitalisations; these are discussed in more detail below.

1.11.1 Strengthening local pharmacovigilance centres and ADR reporting systems

One of the foundations of identifying and managing ADRs is an effective ADR monitoring and reporting system. However, there is a lack of well-established national and local surveillance systems, especially in developing countries, with spontaneous ADR reporting remaining consistently poor, largely due to a lack of education and strong ADR reporting system (214). Hence, encouraging and improving levels of ADR monitoring and reporting represents a major component in a strategy for detecting and preventing ADRs through:

- improving education and changing attitudes about ADR reporting;
- greater involvement of pharmacists and multi-disciplinary teams;
- strengthening drug and therapeutic committees; and
- formation of more localised pharmacovigilance centres.

On the other hand, implementing a mandatory ADR reporting system that encourages reporting and safeguards healthcare providers from repercussions creates an environment that is more insightful for reducing the prevalence of ADRs on the healthcare system. Interestingly, studies suggested that decentralised, interactive pharmacovigilance centres might improve levels of ADR reporting (215, 216). The risk of ADRs have been minimised through pharmacy-led effective drug information provision, along with continuing education regarding medication safety and quality use including herbal and OTC medications (217, 218). Through establishing and strengthening of the existing local pharmacovigilance centres, the perceived barriers and difficulties in early identification and reporting of ADRs can be overcome.

1.11.2 Preventing drug interactions

Most drug-drug interactions and subsequent ADRs involve commonly used medications. It has been reported that drug interactions were a major cause of significant ADR-related hospital

admissions (33). The risk of ADRs due to drug-drug interactions is substantially higher when more medications are being prescribed. For example, bleeding with warfarin therapy is increased with co-administration of NSAIDs, omeprazole and/or statins (219). Hospitalisation for hypoglycaemia was six times more likely with concomitant administration of glyburide and trimethoprim-sulfamethoxazole; digoxin toxicity was twelve times more likely with clarithromycin; and hyperkalaemia was twenty times more likely with concomitant administration of ACE inhibitors and potassium-sparing diuretics than individual drugs as reported by Juurlink et al. (220). Therefore, emphasis should be placed on individual drug pharmacokinetics/pharmacodynamics and patient conditions to identify drug interactions through clinical judgement and/or use of online drug interaction checkers, like Lexi-Interact Online, and Micromedex-2 software for subsequent prevention of ADR-related admissions (221, 222).

1.11.3 Pharmacy/pharmacist-based interventions

There are different forms of pharmacy/pharmacist-based interventions. These include ongoing drug therapy monitoring, which is a process in which pharmacists actively review patients' records, identify and resolve drug therapy problems such as ADRs, and communicate with prescribers when problems occur (223). In contrast, therapeutic drug monitoring (TDM) is the clinical practice of measuring specific drugs at designated intervals to maintain a steady concentration in a patient's bloodstream, thereby optimising safe, effective therapy and individualising dosage regimens (224). TDM is employed mainly for drugs with narrow therapeutic ranges, marked pharmacokinetic variability, target concentrations that are difficult to monitor, and known to cause adverse effects. However, drug therapy monitoring using blood samples is not feasible for routine clinical practice due to economic, ethical and clinical points of view.

Alternatively, pharmacist-centred ongoing drug therapy monitoring processes (in some conditions it includes TDM) include three steps, which are reported to prevent drug-related problems such as ADRs (225). The first step is enhancing active participation of patients in their medication management and their own health decisions through education about their drug therapy, potential ADRs, and actions to take if problems occur. The second step is assessment of patients' drug therapy regularly in order to ensure that patients take their medications as prescribed, proactively identify and resolve ADRs as they occur, and assess therapeutic effectiveness. The third step is ensuring that appropriate laboratory tests that can objectively rule-out or rule-in suspected ADRs are done, assessed, and adjustment of drug therapy is performed accordingly.

Medication reconciliation involves the process of avoiding such unintentional medication discrepancies with subsequent reduction in medication errors and ADRs across transitions in the patient care process (226). This is achieved through reviewing their complete medication regimen at the time of admission, transfer, and discharge, and comparing it with the regimen being considered for the new setting of care. Patients often receive new drugs or have variations made to their existing drugs at the times of transitions in the care process - upon hospitalisation, transfer from one unit to another, or discharge from the hospital to home or referral to another facility. During the transition processes, unintentional changes occur frequently for a variety of reasons, such as hospital-based clinical practitioners not being able to easily identify patients' complete medication lists before admission or being uninformed of recent medication changes. As a result, the new medication regimen prescribed at the time of discharge may unintentionally omit needed medications, unreasonably duplicate existing therapies, or contain incorrect dosage regimens. More than 40% of medication errors are believed to result from inadequate medication reconciliation processes during admission, transfer, and discharge of patients (227). About 20% of these medication errors are believed to result in harm (228). The

majority of these errors would be averted if medication reconciliation processes in general, or pharmacy-led medication reconciliation interventions in particular, were in place (229). In addition, a 2016 systematic review by Mekonnen et al. (229) found that pharmacist-led medication reconciliation processes could prevent medication discrepancies and subsequently ADRs at hospital admissions.

Proactive pharmacy-led interventions such as medication reviews and community pharmacist interventions also help in preventing ADRs, due to pharmacists' expertise in pharmacotherapy, adverse effects and clinical use of medications. Recent meta-analyses (230, 231) revealed that pharmacist-led interventions, such as medication review, that involved a number of implicit structured methods to identify drug-related problems or a combination of explicit and implicit approaches including involvement in ward rounds, have reduced unplanned hospital admissions and ADRs. On the other hand, Home Medicines Reviews conducted by an accredited pharmacist in the patient's home have shown good evidence to support the role of pharmacists in addressing the drug burden index and the medication appropriateness index (232). Moreover, pharmacist-led nursing home medication reviews have reduced polypharmacy with a subsequent reduction in drug burden index and cost (233-235). Therefore, pharmacist-led interventions designed to optimise medication use have a key role to reduce the risk of ADRs. Effective communication among multi-disciplinary teams including physicians, clinical pharmacists and nurses with integral parts in providing clinical services have been shown to reduce medication errors and inappropriate medication use with subsequent improvements in the occurrence of ADRs (215, 236).

1.11.4 Use of clinical tools

The use of explicit clinical tools such as Beers, STOPP (screening tool of older persons' potentially inappropriate prescriptions) and START (screening tool to alert doctors to right

treatment) criteria can help identify medications causing ADRs and result in significant reduction of the ADRs (237, 238). The Beers criteria are the most commonly used criteria to assist clinicians in preventing ADRs in older adults (239, 240). According to 2015 updated Beers criteria, medication classes are divided into three categories based on the updated criteria (239). These included potentially inappropriate medications and classes to avoid in older adults, potentially inappropriate medications and classes to avoid in older adults with certain diseases and syndromes that the drugs listed can exacerbate, and finally medications to be used with caution in older adults. Similarly, potentially inappropriate medications, as defined by 65 clinically important STOPP criteria, are significantly associated with avoidable ADRs that contribute to urgent hospitalisation in older persons (241). Moreover, the STOPP and the START criteria represent the more common avoidable instances of inappropriate prescribing in older persons in day-to-day clinical practice. The START criteria consist of 22 evidence-based prescribing indicators for commonly encountered diseases in older persons, which have been validated in the same fashion as the STOPP criteria and represent the more common instances of inappropriate omission of potentially beneficial medications (242). On the other hand, use of implicit criteria, such as the medication appropriateness index (MAI) is the most common approach that predicts adverse drug events in older adults (243-245).

1.11.5 Effective use of informatics and computerised systems

Effective use of health informatics and computerised systems such as electronic databases and the internet, enables healthcare facilities to utilise software programs and facility-wide systems that prompt warnings for potential ADRs when medical practitioners order medications for patients (246). These prompt warnings often include consideration of a patient's age, weight, underlying clinical conditions and renal and liver function, providing a more holistic approach to creating a suitable drug treatment plan.

Rommers et al. (207) reported that Computerised Physician Order Entry (CPOE) and Clinical Decision Support Systems (CDSSs) are two types of computer-based intervention that have shown benefits beyond medication safety, although they have some limitations. CPOE is a computerised system where the prescriber accomplishes medication ordering online using computer programs whereas CDSS is a system used to provide computerised advice while prescribing and usually works in conjunction with CPOE. CDSS has the ability to execute automatic drug allergy and drug interaction checks, and advise on drug doses and routes. A study on the implementation of CPOE showed a significant decline in preventable, potential adverse drug events, including ADRs, from approximately 11 events per 1000 patients days to 5 events (247) and the number of transcription errors reduced by 84%. However, there is still limited evidence available to show these interventions reduce the occurrence of ADRs (248). Therefore, improving access to various sources of information and hand-held devices with daily free database updates would aid improved prescribing and allow rapid checking of potentially hazardous drug interactions (249). In addition, adequate induction and staffing of medical practitioners regarding effective use of electronic databases coupled with strengthening of effective communication among multi-disciplinary teams help reduce the risk of occurrence of ADRs.

1.11.6 Highlighting patients at risk using predictive parameters

In addition to focusing on processes of care, highlighting patients at risk of ADRs can help in preventing ADR-related hospitalisations. More importantly, the central concept in developing a risk prediction model is the utilisation of predictors or risk factors in providing estimates of individual probabilities of risk and benefits. Identifying patients at high risk of ADR-related hospitalisation depends on several risk factors, including socio-demographics, genetic predisposition, drug-related and clinical factors; these factors can be used to target

individualised intervention. For instance, ADR predictive factors might vary due to variations in therapeutic options used with regard to differences in disease distribution, population socio-demographics (9, 14, 23, 100), healthcare systems (104) and ethnic origin (168, 250). Several risk factors have been identified by previous studies (14, 208); however, medical practitioners often lack awareness of predictors of ADR-related hospitalisations or factors contributing to ADR-related deaths (251, 252).

A very recent study from Australia by Parameswaran et al. (213) identified five independent predictors of ADR-related hospitalisations in elderly patients. These include drug changes in the preceding 3 months, presence of renal failure and dementia, use of antihypertensives and anticholinergics; these variables were used to derive an ADR prediction score. According to this study, the predictive ability of the score, assessed from calculation of the area under the receiver operator characteristic (AUROC) curve, was 70% (95% confidence interval (CI) 65–75%). Another study from Germany (14) that aimed to characterise risk factors associated with ADRs established five variables as independent predictors of ADRs: increased body temperature, low thrombocyte levels, low erythrocyte levels, multiple drug use, and female sex. According to this study, the risk prediction ability of the model based on the AUROC curve was 80% with a sensitivity of 64% and specificity of 86%. These risk factors were developed based on data from 907 patients with a mean age of 60 years old. Although there are few studies on prediction of ADR-related hospitalisations in adults, existing evidence suggests that ADR-related hospitalisation risk prediction models are a possible solution for early identification of and intervention for elderly patients who are at higher risk for ADRs.

1.12. Ethiopian healthcare system

The Ethiopian healthcare system is a three-tier healthcare delivery system. The first level, the district health system, comprises a primary hospital (with population coverage of 60,000-

100,000 people), health centres (15,000-25,000 population) and their satellite health posts (3,000-5,000 population) that are connected to each other by a referral system. A primary hospital, health centre and health posts form a primary health care unit (PHCU) with each health centre having five satellite health posts (253).

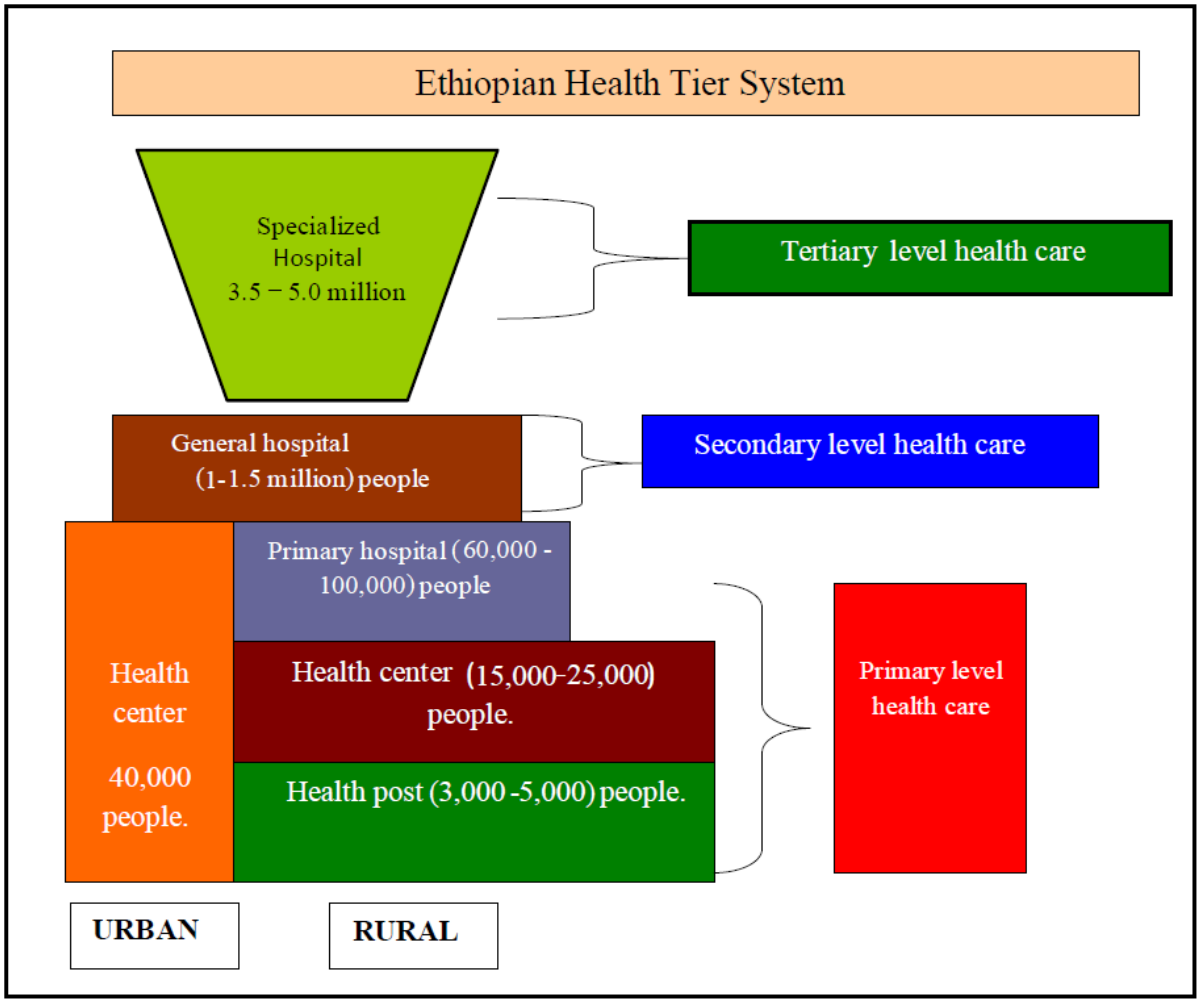


Figure 1. 7 Adapted from the Ethiopian Health Sector Development Plan 2010-2015 (253)

The Health Extension Program in the primary healthcare system (at Health Post level) is an innovative community-based health program that has enabled Ethiopia to increase primary health care coverage from 76.9% in 2005 to 90% in 2010 (254). Currently there are more than 38,000 health extension workers (HEWs) in more than 16,000 health posts. Households are

organised into a health development army (HDA) for participatory learning and action meetings to actively engage the community in the Health Extension Program (255).

The HEWs are trained to implement a Health Extension Package (HEP) of 16 healthcare activities at the kebele (village) level. All HEWs are women, at least 18 years of age, with a minimum of 10th grade education and recruited from the communities in which they will work. HEWs must complete a one-year course of instruction and field training, provided by Technical and Vocational Education Training Schools (TVETs), operated by the Ministry of Education. Upon completion of training, HEWs are assigned, in pairs, to a kebele (village) where they staff health posts and work directly with individual families. Health posts, therefore, are the first level of healthcare for the community, emphasising preventive care. HEWs spend 75% of their time visiting families in their homes and performing outreach activities in the community. The remaining 25% is spent providing services at the health posts, including immunisations and injectable contraceptives, among others. The 16 components of HEPs, as a preventive health program, promote four areas of care: disease prevention and control, family health, hygiene and environmental sanitation, and health education and communication. These include HIV/AIDS and other STIs and TB prevention and control, malaria prevention and control, first aid emergency measures, maternal and child health, family planning, immunisation, nutrition, adolescent reproductive health, excreta disposal, solid and liquid waste disposal, water supply and safety measures, food hygiene and safety measures, healthy home environment, personal hygiene and health education and communication (256).

The secondary level in the tier is a general hospital with population coverage of 1-1.5 million people; and the tertiary level is a specialised hospital that covers a population of 3.5-5 million. According to the Ethiopian healthcare system, referral can be vertical from the lower end of the health tier system to the higher ones. It can be horizontal between similar levels of facilities in the interest of patients for cost, location and other reasons. Referrals can also be diagonal

when a lower level health facility directly refers patients to a specialised facility without necessarily passing through the hierarchical system. Overall, referrals can be among public, private, community based and other traditional and alternative medicine practitioners and sometimes social services are also included (257).

As a tertiary level hospital, Jimma University Specialised Hospital is the major public teaching and referral hospital with a capacity of 600 beds in Southwest Ethiopia. The hospital provides both general and specialised services for approximately 200,000 patients each year. The hospital delivers a range of services on an outpatient, inpatient and emergency basis in various clinical departments including internal medicine, surgery, obstetrics and gynaecology, paediatrics, anaesthesia, dentistry, ophthalmology, psychiatry, pharmacy, laboratory medicine and radiology (258).

1.13. ADR reporting system in Ethiopia.

Under the Ethiopian Federal Ministry of Health, the Food, Medicine, Healthcare Administration and Control Authority (FMHACA) carries out post-marketing surveillance of pharmaceuicals. The primary role and mandate of FMHACA is to ensure that marketed medicines are safe and of good quality for the public. The authority has the responsibility to investigate safety concerns and take action to prevent and minimise medicine-related harm. FMHACA consults the national drug advisory committee that is composed of mutidisciplanary health professionals team to evaluate drug safety concerns and recommends possible action to be taken by the authority. According to the FMHACA, all suspected ADRs, detected medication errors or product quality defects should be reported to the pharmacovigilance centre at FMHACA via the yellow prepaid report form available at each health facility (from primary to tertiary level), via telephone or via email. When the reports have been received by FMHACA, an acknowledgement letter is sent to the reporter and follow-up questions need to be answered. The ADR report details collected at the FMHACA level will electronically be sent to the WHO

Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) in Sweden (259).

There are different stakeholders involved in ADR reporting from the healthcare facility level to the federal pharmacovigilence centre with different roles and responsibilities. These includes, but are not limited to patients and consumers, all healthcare professionals, drug and therapeutic committees (DTCs) and the marketing authorisation holders, such as pharmaceutical industry, drug and chemical importers, wholesalers and distributors. The DTC is a technical working group established at each health facility level with representative members from each department with the aim of managing medication use problems including assessment of ADEs, implementing programs to track ADEs, and designing interventions, methods and procedures that will prevent the occurecne of ADEs (259).

Ethiopia established its own pharmacovigilance database management system under FMHACA in 2002 (260). Following this, Ethiopia became a full member of the WHO program for international drug monitoring (261), however, the ADR reports received from the centre are limited in numbers. For instance, a total of 249 ADR cases were reported between 2002 and 2007 with an average of 0.5 ADR cases per million population per year. More than half (63%) of the cases were from health facilities in the capital city. Most (76.0%) of the ADRs were reported by physicians. More than two-thirds (70.0%) of the ADRs were associated with antiretroviral drugs (260). Spontaneous reporting of ADRs is a significant activity to improve the safety of medicines and health care professionals are pivotal players in spontaneous reporting of ADRs. However, surveys conducted at different times and places revealed that the majority of healthcare professionals have inadequate levels of knowledge and practice towards ADR reporting although they have positive attitude for reporting (262-264).

1.14. Definitions and methods used in this study

The discrepancy in terms is a major source of error when comparing studies and their methodologies. A widely accepted, formal definition would allow for better comparison between ADR-related hospitalisation studies and their impact worldwide. For the purposes of this study, we adopted the WHO ADR definition because this definition is intended to include all doses used clinically but exclude deliberate overdose and has been used widely in ADR studies over the last 40 years (22, 23). Additionally, compared to other definitions described in Section 1.2, the WHO ADR definition comprehensively describes ADRs that encompasses all ADRs no matter their severity level.

The Naranjo method was chosen to assess ADR causality in this study because it has been widely used in observational studies because of its simplicity to apply and its objective measurement (89). In addition, the Naranjo ADR Probability Scale is quick to complete when compared to other more comprehensive and detailed methods. The Naranjo algorithm has the advantage of a reduction in inter-rater disagreement and uncertainty in evaluation of potential ADRs and therefore it is commonly utilised by pharmacovigilance centres of several nations (265).

The severity of ADRs in this study was assessed using the Hartwig et al. severity scale because it is simple, easy to use, has clear definitions, and it has been applied in prospective study of ADR-related hospitalisations (47). Additionally, this scale uses the principles of ADR severity assessment based on length of stay, treatment requirement, and the patient's prognosis that are important parameters to characterise the most common ADRs of public health relevance, particularly in resource-limited settings, such as Ethiopia.

Although some ADRs are unavoidable and occur even with the most extraordinary precautions in place, a large proportion of ADRs may be preventable (266). The Schumock and Thornton

criteria was chosen for assessing ADR preventability in this study because it is widely used in observational studies and clinically focussed to assess avoidability of an ADR. According to Schumock and Thornton criteria, preventable ADRs include but are not limited to: allergic reactions where the allergy is previously known and/or documented; avoidable dose-related reactions; idiosyncratic reactions that have occurred previously; ADRs secondary to drug interactions; and ADRs associated with inappropriate compliance, prescribing, or administrations.

1.15. Rationale of the study

ADRs are a major health problem for the public (267) and are associated with morbidity, hospitalisation, mortality and additional costs (10). Studies have reported that the prevalence of ADR-related hospitalisation varies from 0.2% (28) to 54.5% (29). Severe ADRs were an important reason for extensions of the hospital stay in approximately 20.0% of patients (41), and can cause life-threatening effects and admission to intensive care unit in up to 19.0% of the ADR cases (40, 42, 43). Studies focusing on predictors of ADR-related hospitalisations are from developed countries and have focussed on the older population (9-11, 14). However, there are significant variations between the populations of developed and developing countries with regard to disease distribution (9, 14, 23, 100), population demographics (9, 14, 23, 100), healthcare systems (104), complexity of diseases, medications prescribed (9, 14, 94), and ethnic origin (168, 250).

Despite reporting of the burden of diseases, all-cause mortality, medication use patterns and associated adverse events, to our knowledge, there are no studies focusing on ADR-related hospital admissions and mortality in Ethiopia. However, there are number of factors suspected to increase the risk of ADR-related hospital admissions. These include, but are not limited to, a higher proportions of patients who take anti-TB agents and ART (268),

traditional remedies (269), and concomitant anti-TB and antiretroviral therapies with overlapping adverse effects (270) than in developed countries. In addition, there is a higher proportion of the slow acetylator phenotype among patients on ART and anti-TB drugs that increases susceptibility to ADRs (271). Moreover, there are higher frequencies of genetic variants conferring increased risk for ADRs for commonly used drugs treating cancer, HIV/AIDS and tuberculosis (271, 272) in people of African descent. Furthermore, there are higher proportions of patients with concomitant infectious and non-communicable diseases taking multiple medications for long-term or life-long therapy than in developed countries (23, 199, 200, 273, 274). Unlike developed countries, there is substantial all-cause mortality rate among patients presenting to emergency departments (275), a high rate of mortality among HIV/TB co-infected patients on drug therapy (276), a less health-literate population (277), a lesser ability to provide healthcare (278), and a higher prevalence of malnutrition (279, 280).

Given ADRs are associated with substantial clinical, economic, and humanistic problems in the healthcare system, our research aimed to address a gap in knowledge to allow developing (and developed) countries to better understand and address the level of problem. Considering the overall burden of ADR-related hospitalisation and mortality, the application of prevention strategies to prevent ADRs is of great importance, thus, this research intended to identify key areas for intervention to help reduce the ADR-related hospitalisation and mortality. To address the gaps in knowledge, the level of the problem and intervention areas, especially in developing countries, we conducted a review of the current literature followed by a prospective observational study. The review compared the prevalence and contributing factors of ADR-related hospitalisations in developed and developing countries. Despites the differences in the healthcare system, patient demographics, disease distribution and drug therapy used, the review showed that the burden of ADR-related hospitalisations and mortality is comparable between

developed and developing countries. Following this, prospective observational studies determined the prevalence of ADR-related hospitalisation and mortality in adults; identified drugs commonly implicated in hospitalisation and mortality; characterised the severity and patterns of ADRs; highlighted the patients at higher risk for ADR-related hospitalisation using an ADR risk prediction model and determined preventability of ADRs.

1.16. Aims

The overall aim of this thesis was to investigate ADR-related hospitalisation and mortality in Ethiopian adult patients.

Specific objectives were to:

- Summarise and compare existing literature on the prevalence and contributing factors of ADR-related hospitalisation between developing and developed countries.
- Characterise the ADR types, severity, preventability and the drugs implicated in hospitalisation and identify predictors of ADR-related hospitalisation.
- Determine the mortality rate attributable to ADRs in patients presenting to hospital, identify drugs implicated in the ADR-related deaths and identify factors contributing to ADR-related mortality.
- Determine the prevalence, severity and clinical patterns of DIH and identify commonly implicated drugs in DIH-related hospital admissions.

Chapter Two

2. Adverse drug reaction related-hospitalisations in developed and developing countries: A review of prevalence and contributing factors

2.1 Abstract

Adverse drug reactions (ADRs) are one of the leading causes of hospital admissions and morbidity in developed countries and represent a substantial burden on health care delivery systems. However, there is little data available from low and middle-income countries. This review compares the prevalence and characteristics of ADR-related hospitalisations in adults in developed and developing countries; including the mortality, severity, and preventability associated with these events, commonly implicated drugs and contributing factors. A literature search was conducted via PubMed, Scopus, Web of Science, Embase, ProQuest, and Google Scholar to find articles published in English from 2000 to 2015. Relevant observational studies were included. The median (with interquartile range (IQR)) prevalence of ADR-related hospitalisation in developed and developing countries were 6.3% (3.3%-11.0%) and 5.5% (1.1%-16.9%), respectively. The median proportion of preventable ADRs in developed and developing countries were 71.7% (62.3%-80.0%) and 59.6% (51.5%-79.6%), respectively. Similarly, the median proportion of ADRs resulting in mortality in developed and developing countries were 1.7% (0.7%-4.8%) and 1.8% (0.8%-8.0%), respectively. Commonly implicated drugs in both settings were antithrombotic, non-steroidal anti-inflammatory, and cardiovascular drugs. Older age, female gender, number of medications, renal impairment, and heart failure were reported to be associated with an increased risk for ADR-related hospitalisation in both settings while HIV/AIDS was implicated in developing countries only.

The majority of ADRs were preventable in both settings, highlighting the importance of improving medication use, particularly in vulnerable patient groups such as the elderly, patients with multiple comorbidities, and those in developing countries with HIV/AIDS.

2.2. Key points

Reviews comparing the prevalence of ADR-related hospitalisations and contributing factors among adults in developed and developing countries were uncommon.

ADR-related hospitalisations from the influence of HIV/AIDS and other infectious diseases and their associated medications are the main difference in developing countries.

There was wide variation in the prevalence of ADR-related hospitalisations among studies due to lack of golden standard tools for causality assessment, severity scaling and preventability classification.

The use of a standardised approach for assessment of ADR causality, severity, and preventability would greatly contribute towards an improved understanding of the global nature and extent of ADRs.

2.3 Introduction

The World Health Organisation (WHO) defines an adverse drug reaction (ADR) as: "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" (21). ADRs are a major health problem for individuals and the public in general (267); studies from different parts of the world have reported that the overall prevalence of ADR-related hospitalisation varies from 0.2% (28) to 54.5% (29).

The wide variation in the prevalence of ADR-related hospitalisations among studies is due to differences in disease distribution and population characteristics (9, 14, 23, 100), healthcare systems (104) and ethnic origin (168, 250). In addition, complicated case management with multiple medications, mainly in studies from developed countries (9, 14, 94, 281), and differences in study designs (retrospective vs prospective) (282) have contributed to the variations in reported prevalence. Moreover, differences in the definition of ADR used (24, 283) and ADR causality assessment methods (84, 88) have contributed to these variations.

Between 1998 and 2015, six reviews reported a prevalence of ADR-related hospitalisation in adult populations of 0.16% to 41.3% (56, 106, 117, 284-286). There were, however, a number of limitations to these reviews. Some reviews applied a search strategy using a limited number of key words and search engines. As a consequence, relevant studies may have been excluded. In addition, some reviews provide limited information about the method used for ADR detection, causality assessment, proportion of severe and preventable ADRs, ADR-related mortality, and specific risk factors contributing to the occurrence of ADRs. The reviews commonly included studies from developed countries, focusing on mainly the elderly and paediatric groups.

In developing countries, the risk of ADR-related hospitalisation is becoming a major health concern as a result of increasing numbers of patients presenting with common morbidities such as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and tuberculosis comorbid with other chronic illnesses (23, 199, 200, 273). The specific concerns of the developing world (where majority of the population are young adults (287)) have not been considered in previous reviews. The use of complex and relatively new therapies in these settings may make detection and reporting of ADR-related burden more crucial than before (199, 200). Similarly, a growing attention to chronic diseases and their complicated management with multiple medications presents an important clinical burden for developing healthcare settings (273). In addition, most developed countries with effective regulatory systems and market control (e.g. United States of America, European Union, Australia, Canada, Japan, New Zealand) currently have a very low proportion, i.e. less than 1% of market value of counterfeit medicine, however, in many developing countries of Africa, parts of Asia, and parts of Latin America have areas where between 10% and 30% of the medicines on sale can be counterfeit (288). We therefore undertook a review with a focus on comparing the prevalence of ADR-related hospitalisation, mortality, severe reactions and commonly implicated drugs among adults in developed and developing countries. In addition, we reviewed information on contributing risk factors, and the prevalence of preventable ADR-related hospitalisations which represent an important target for intervention.

2.4 Methods

A literature search focusing on ADR-related hospitalisations was conducted via PubMed, Scopus, Web of Science, Embase, Proquest, and Google Scholar to find articles published in English from 2000 to 2015 using key terms: “adverse drug reactions”, “drug related side effects”, “adverse drug events”, “adverse drug effects”, “medicine-related problems”, “drug-

related problems", "drug toxicity", "drug therapy problems", "adult patients", "elderly patients", "older patients", "geriatric patients" combined with "hospitalization", "emergency admission", "hospital admission", "acute care admission", and "hospitalisation". The search was conducted between December 2014 and December 2015.

Observational studies that estimated the prevalence of ADRs prospectively and/or retrospectively were included. We excluded studies which focused on ADRs and adverse drug events (ADEs) in relation to a specific drug or drug group (e.g. anticoagulants); a specific clinical condition (e.g. renal failure); those investigating ADR-related hospital readmissions; those carried out in intensive care unit; and studies reporting medication errors, therapeutic failures, non-compliance, accidental and intentional poisoning, and drug abuse. Study participants included were patients (age ≥ 15 years) admitted due to ADRs. For studies that included all ages in the study population, only data for patients aged 15 years and over were included in this review. For inclusion in this review, studies had to include an explicit definition of what was considered as an ADR (e.g. WHO (283) or Edwards and Aronson(24) definition), an explicit assessment of causality (e.g. Naranjo (88) or WHO(283)), a clear description of the method used for ADR identification, and exploration of factors associated with the risk of ADR. Duplicate studies were removed by screening on title, abstract, and full text.

For data analysis, we categorised ADRs as either severe or non-severe based on the information obtained in the selected studies, according to the classifications of Hartwig *et al.* (46) and Morimoto *et al.* (27). Severe ADRs were those leading to hospital admissions and prolonged existing hospitalisation, leading to permanent defects or life threatening complications, demanding a dosage reduction and therapy cessation, or requiring additional therapeutic measures or specific treatment (27, 46), whereas others were non-severe. Similarly, we categorised ADRs as preventable and non-preventable according to the details provided, using the Hallas *et al.* (202) and Schumock *et al.(201)* classification criteria. ADR-related mortality

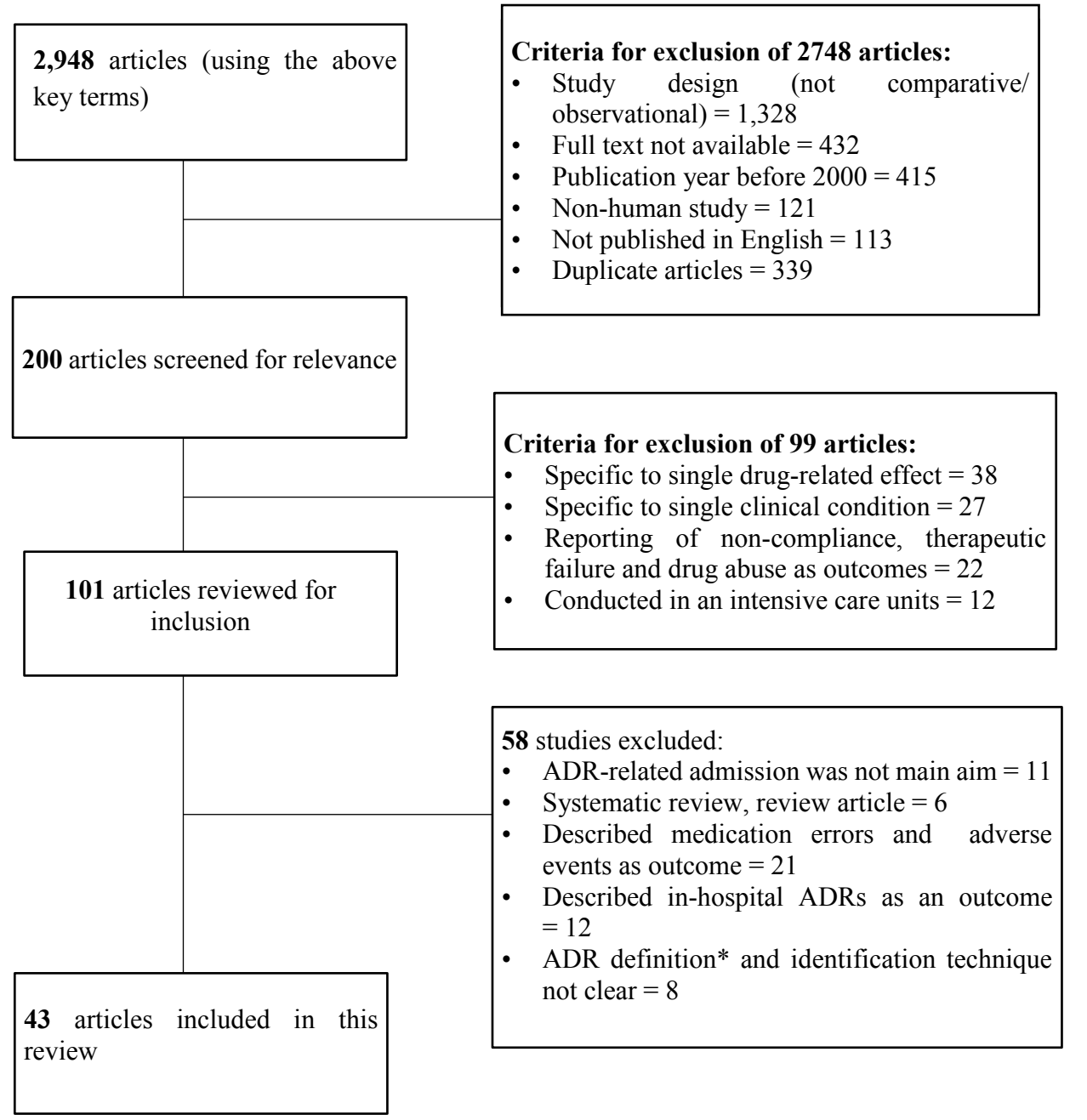
was recorded from ADRs leading to death (fatal ADRs). ADRs were classified as type A (dose dependent, augmented pharmacological and predictable reactions) and type B (bizarre, dose independent and non-predictable reactions) according to the Rawlins and Thompson classification method (75). We categorised countries into developing or developed on the basis of socio-economics, per capita income, industrialisation, literacy rate, and living standards published by the World Bank (289). ADR-related admission was defined as ADRs which were assessed as being implicated directly as a reason for admission and the ADRs identified at the time of medical admission that have contributed directly or indirectly to the hospital admission.

The following data was extracted:

1. Study characteristics: country; year conducted; study design (prospective or retrospective); number of study participants.

2. Identification of ADR-related burden: prevalence of ADR-related admission; associated mortality; proportion of severe and preventable ADRs; ADR identification techniques.

3. Information relating to the ADR: implicated drug(s); commonly reported ADRs; associated risk factors (including age, gender, polypharmacy, co-morbidity); ADR types.



*Indicates ADR definitions used in this review: WHO definition: "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" [21].Edwards and Aronson definition: "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product "[24].

Figure 2. 1 Flow chart showing inclusion and exclusion of articles used in this review

2.5 Results

Based on the inclusion and exclusion criteria, 43 articles exploring ADR-related hospitalisations in more than 2.1 million adult patients (2,009,751 patients in developed countries and 131,649 patients in developing countries) were identified (Table 2.1). The study designs varied from a large retrospective hospital database review of 668,714 patients(12) to a small prospective cross-sectional clinical study of 106 patients. Thirty-one studies were conducted solely in an adult population with the remainder in all age groups. The majority of the ADRs (68.2%) were type A and therefore most were potentially avoidable. Out of 43 studies included in this review, 30 were conducted in developed countries (out of which 28 were in Europe) and 13 studies were conducted in developing countries.

2.5.1 Prevalence of ADR-related hospitalisations and deaths

There was wide variation in the reported prevalence of ADR-related hospitalisations in the 43 selected studies, from 0.2% to 54.5%. The median prevalence of ADR-related hospitalisation of overall studies was 6% (interquartile range (IQR), 2.7%-11.0%). The prevalence in developed countries ranged from 0.5% to 37.5% with the median of 6.3 % (IQR, 3.3%-11.0%), while in developing countries it ranged from 0.2% to 54.5% with the median of 5.5% (IQR, 1.1%-16.9%) (Figure 2.2 and Table 2.3).

The prevalence of ADR-related hospitalisations were relatively more consistent among studies in developed countries than developing countries (Figure 2). Irrespective of the socio-economic background of the countries, prospective studies were associated with a higher ADR prevalence than retrospective studies (median of 6.5% (IQR, 3.8%-11.5%) versus 4.2 % (IQR, 1.4%-11%)).

Out of 43 studies included in this review, only 19 reported on the severity level of the ADRs leading to hospital admissions. From these studies, the median proportion of severe ADRs

leading to hospitalisation was 20% (IQR, 9.8%-24.0%) in developed countries and 10.0 % (IQR, 5.7%-24.0%) in developing countries The minimum and maximum proportions of severe ADRs with regard to the countries were 3.6% in 4,403 Spanish patients (retrospective study) (98) and 62.0% in 3,190 German patients (prospective study) (94). Irrespective of socio-economic background, severe ADRs were reported to be common in older patients with greater comorbidity (9) and who were taking more medications (9, 281). Across all studies, the majority of ADR-related admissions were preventable. The proportion of preventable ADR-related admissions ranged from 20.1% of 57,000 German patients (58) to 92% of 4,403 Spanish patients (98) with a median proportion of 71.7 % (IQR, 62.3%-80.0%) in developed countries and 59.6 % (IQR, 51.5%-79.6%) in developing countries. In the majority of cases, prospective observational studies were associated with a higher median proportion of severe ADR-related admissions than retrospective studies (17.2% (IQR, 5.5%-32.2%) versus 5.7 % (IQR, 9.8%-24.0%)) (Table 2.3). Similarly, preventable ADR-related admissions were higher in prospective studies (75% (IQR, 56.3%-84.5%) versus retrospective studies 30% (IQR, 20.1%-62.3%)).

Table 2. 1 Characteristics of selected studies examining ADR-related admissions in study population of this review

Reference	Study design	Study population & sample size	Country & year study conducted	Prevalence of ADR related admission	Proportion of severe ADR	Proportion of preventable ADR	Proportion of ADR related mortality	Drug classes reported to cause ADR-related admissions
Ahern F *et al.* (30)	Prospective observational	Adults (n=856)	Ireland, 2010	8.8%	NR	57.3%	NR	Cardiovascular and CNS drugs
Alexopoulou A *et al.* (16)	Prospective observational	Adults (n=548)	Greece, 2008	12.8%	18.6%	NR	NR	NSAIDs, diuretics, antithrombotics, hypoglycaemic agents
Alvarez PA *et al.* (35)	Pharmacovigilance approach	Adults (n=1045)	Argentina, 2010 to 2012	10.7%	4.0%	85.7%	8.0%	NSAIDs and antiplatelets
Budnitz DS *et al.* (290)	Retrospective record review	Adults (n=12,666)	USA, 2007 to 2009	37.5%	NR	NR	NR	Antithrombotic and anti-diabetic agents
Brvar M *et al.* (39)	Retrospective review of medical records	Adults (n=520)	Slovenia, 2006	5.8%	NR	90.0%	0.0%	NSAIDs, aspirin, warfarin
[a]Carrasco-Garrido P *et al.* (15)	Retrospective, descriptive, epidemiologic study	All age groups (n= 350,835)	Spain, 2001 to 2006	1.6%	NR	NR	5.6%	Antineoplastics and immunosuppressives
Chen YC *et al.* (37)	Prospective observational study	Adults (n=58,569)	Taiwan, 2009 to 2010	0.8%	24.0%	73.4%	10.0%	Cardiovascular agents
Chen YC *et al*. (291)	Case-control study	Adults (n=20,628)	Taiwan, 2009 to 2010	1.4%	NR	NR	NR	Anti-diabetics, analgesics, cardiovascular drugs and anticoagulants
Franceschi M *et al.* (93)	Prospective observational study	Adults (n=1756)	Italy, 2004 to 2005	5.8%	NR	76.5%	NR	NSAIDs, oral anticoagulants, low-dose aspirin, and digoxin

Table 2.1 Characteristics of selected studies continued……

Reference	Study design	Study population & sample size	Country & year study conducted	Prevalence of ADR related admission	Proportion of severe ADR	Proportion of preventable ADR	Proportion of ADR related mortality	Drug classes reported to cause ADR-related admissions
Green CF *et al.* (32)	Review of patient medical records	Adults (n=200)	UK, 2000	7.5%	NR	66.7%	1.0%	NSAIDs and cardiovascular agents
Hartholt KA *et al.* (103)	Retrospective record review	Adults (n=361,760)	Netherlands, 1981-2007	17.6%	NR	40.0%	NR	Agents affecting blood constituents, cardiovascular drugs and analgesics
Hofer-Dueckelmann C *et al.* (94)	Prospective observational study	Adults (n=3190)	Germany, 2011	7.5%	62.0%	NR	NR	Diuretics and anticoagulants
Hopf Y *et al.* (95)	Prospective observational study	Adults (n=1,101)	Scotland, 2006	2.7%	NR	83.3%	6.7%	Antiplatelets and NSAIDs
Lagnaoui R *et al.* (292)	Prospective cohort study	Adults (n=444)	France, 2000	7.2%	NR	80.0%	None were fatal	Antihypertensives, psychotropics, insulin, antineoplastics, anti-infectives
Mannese CK *et al.* (52)	Prospective cross sectional	Adults (n=106)	Netherlands, 1994	12.0%	24.0%	NR	NR	Oral anticoagulant
Matanovic SM *et al.* (293)	Prospective and observational study	Adults (n=454)	Croatia, 2009 to 2010	11.0%	NR	NR	NR	NSAIDs and benzodiazepines
McDonnell PJ *et al.* (33)	Retrospective chart review	All ages (n=437)	USA, 1998 to 1999	36.2%	24.0%	62.3%	NR	Chemotherapy, anticoagulants and antidiabetics
Mehta U *et al.* (23)	Prospective observational study	Adults (n=665)	South Africa, 2005	6.3%	14.1%	53.0%	1.5%	Antiretroviral drugs, ACE-inhibitors, diuretics, warfarin and NSAIDs
Mjörndal T *et al.* (166)	Patient interview and record review	Adults (n=681)	Sweden, 2002	12.0%	NR	91.0%	NR	NR
[a]Noblat AC *et al.* (66)	Prospective observational study	All age groups (n= 37,658)	Brazil, 2007	0.4%	5.7%	NR	0.5%	Antineoplastic and antibiotics
Olivier P *et al.* (96)	Prospective survey	Elderly (n=789)	France, 2002 to 2003	8.4%	NR	NR	NR	Antibacterials and antithrombotics

Table 2.1 Characteristics of selected studies continued……

Reference	Study design	Study population & sample size	Country & year study conducted	Prevalence of ADR related admission	Proportion of severe ADR	Proportion of preventable ADR	Proportion of ADR related mortality	Drug classes reported to cause ADR-related admissions
Onder G *et al.* (9)	Multicentre pharmaco-epidemiology survey	Adults (n=28,411)	Italy, 1988 to 1997	3.4%	20.0%	75.0%	4.0%	Cardiovascular agents and NSAIDs
[a]Patel H *et al.* (17)	Retrospective review of hospital database	All age group (n= 447, 071)	UK, 1998 to 2005	0.5 %	NR	NR	NR	Cancer chemotherapy, analgesics and cardiovascular drugs
Patel KJ *et al*. (34)	Prospective observational	Adults (n=6899)	India, 2005	6.9%	6.8%	59.6%	0.8%	Anti-tuberculosis drugs, warfarin and chloroquine
Pedrós C *et al.* (98)	Cross sectional study	Adults (n=4403)	Spain, 2009 to 2010	4.2%	3.6%	92.0%	3.2%	RAS inhibitors, oral anticoagulants, antiplatelets and NSAIDs
Pérez Menéndez-Conde C *et al.* (104)	Cross-sectional, prospective and observational study	Adults (n=252)	Spain, 2011	19.4%	20.4%	65.0%	NR	Antineoplastic therapy and immunosuppressants
Pirmohamed, M *et al.* (10)	Prospective observational study	Adults (n=18,820)	UK, 2001 to 2002	6.5%	NR	72.0%	2.3%	Low dose aspirin, diuretics, warfarin, and NSAIDs
Pourseyed S *et al.* (55)	Prospective observational study	Adults (n=400)	Iran, 2004	1.8 %	14.3%	50.0%	4.3%	Antineoplastics, and immunosuppressives
Pouyanne P *et al.* (20)	Cross sectional study	Adults (n=3137)	France,1998	3.2%	NR	NR	0.1%	Cardiovascular agents
Ramesh M *et al.* (42)	Prospective observational study	All age groups (n=3717)	India, 2003	5.5%	10.0%	NR	1.8%	Cardiovascular agents, anti-infectives and NSAIDs
Rottenkolber D *et al.* (58)	Medical record review	Adults (n=57,000)	Germany, 2006 to 2007	3.3%	9.8%	20.1%	1.0%	Antithrombotics, anti-diabetics and diuretics
Ruiter R *et al.* (97)	Review of registry of hospital discharge records	Adults (≥55years)	Netherlands, 2012	1.3%	NR	NR	NR	Anticoagulants, anti-diabetics, salicylates and anti-rheumatics

Table 2.1 Characteristics of selected studies continued……

Reference	Study design	Study population & sample size	Country & year study conducted	Prevalence of ADR related admission	Proportion of severe ADR	Proportion of preventable ADR	Proportion of ADR related mortality	Drug classes reported to cause ADR-related admissions
Sánchez Muñoz-Torrero JF *et al.* (100)	Prospective observational study	Adults (n=405)	Spain, 2009	6.0%	17.0%	NR	1.6%	Antibiotics, enoxaparin, phenytoin and atorvastatin
Schneeweis S *et al.* (105)	Longitudinal population-based study	All age groups (n=41,375)	Germany,1997 to 2000	2.4%	44.0%	79.0%	1.7%	Cardiovascular, antithrombotics, analgesics and anti-rheumatics
Sonal Sekhar M *et al.* (28)	Retrospective record review	Adults (n=575)	India, 2002 to 2009	0.2%	NR	NR	NR	CNS drugs, NSAIDs, antibiotics and anticoagulants
Tipping B *et al.* (109)	Prospective cross sectional study	Adults (n=517)	South Africa, 2005	23.0%	NR	NR	NR	Cardiovascular drugs, anticoagulants and antidiabetics
Tumwikirize WA *et al.* (156)	Prospective observational study	Adults (n=728)	Uganda, 2005	4.5%	No severe ADR	NR	No death	Quinine
van der Hooft CS *et al.* (12)	Retrospective review of hospital discharge record	All age groups (n=668,714)	Netherlands, 2001	1.8%	NR	NR	6.0%	Anticoagulants, cytostatics, immunosuppressives and diuretics
[a]van Der Hooft CS *et al.* (99)	Retrospective cohort study	All age groups (n=3515)	Netherlands, 2003	4.1%	5.7%	30.0%	0.3%	Antithrombotics, cardiovascular and cytostatics
Varallo FR *et al.* (107)	Prospective cross sectional study	Adults (n=248)	Brazil, 2008	46.4%	NR	NR	NR	Cardiovascular drugs and omeprazole
Varallo FR *et al.* (29)	Prospective cross sectional study	Adults	Brazil, 2006	54.5%	NR	NR	NR	Cardiovascular, CNS and respiratory drugs
von Euler M *et al*. (76)	Retrospective review of computerised medical records	Adults (n=168)	Sweden, 2002	11.0%	NR	70.0%	NR	Warfarin, beta-blockers and insulin
Walsh D *et al.* (294)	Prospective observational study	Adults (n=137)	Ireland, 2012	5.1%	NR	71.4%	NR	Antithrombotics and antihypertensives

Notes: [a] In some articles where the prevalence of ADR was not directly reported in the original publication for the study population, it was calculated as the number of patients identified with an ADR out of all included patients. **Abbreviations:** ADR, adverse drug reaction; WHO, World Health Organization; GI, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs; CCB, calcium channel blockers; CNS, central nervous system; NR, Not reported; RAS, renin angiotensin system.

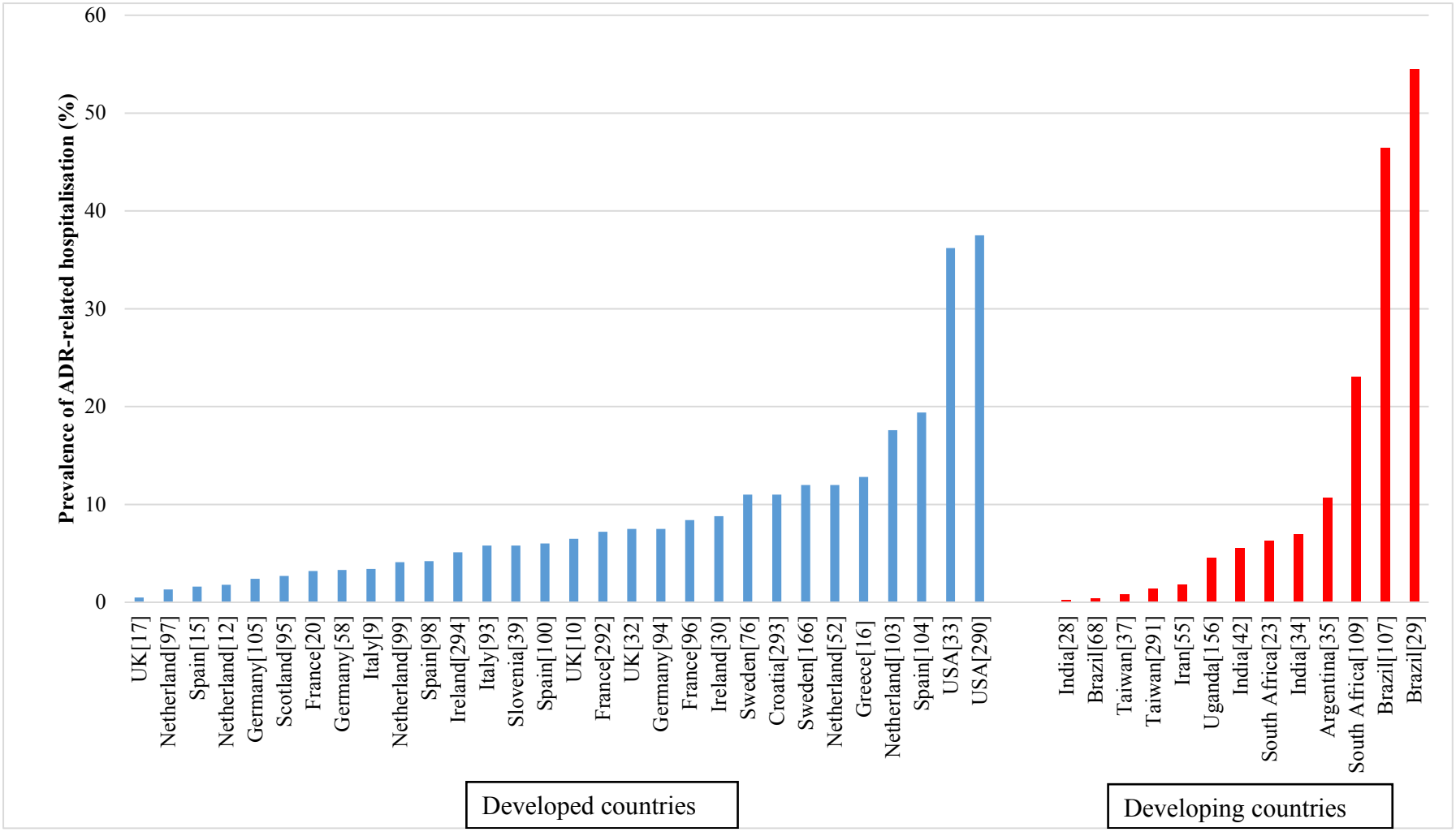


Figure 2. 2 Comparison of the prevalence of ADR-related hospitalisations between developed and developing countries

2.5.2 ADR identification methods/causality assessment techniques

The majority of studies (N=21) used the WHO causality assessment criteria (283) for detection of ADRs, followed by the Naranjo et al. (88) criteria. In 7 studies, ADRs were detected by a team of physicians, clinical pharmacologists, and pharmacists reviewing medical records, discharge summaries or hospital registries (10, 14, 30, 35, 76, 93, 166).

2.5.3 Medications associated with ADR-related hospitalisation

There was considerable variation in medications involved in ADR-related admissions between developed and developing countries, possibly as a result of difference in disease distribution (9, 14, 23, 100), population characteristics (9, 14, 23, 100), healthcare systems (104), and complexity of diseases and medications (9, 14, 94). The majority of the studies found that antithrombotics (oral anticoagulants and antiplatelet agents) (16, 34, 35, 93-97), non-steroidal anti-inflammatory drugs (NSAIDs) (10, 16, 23, 35, 39, 93, 95, 98), and cardiovascular medications (20, 30, 34, 94, 98, 99) were commonly associated with ADR-related hospital admissions, irrespective of the socioeconomic status of the countries. Other implicated medications included anti-infectives (34, 96, 100), antineoplastics, immunosuppressants (12, 15, 104), and antidiabetic agents (16, 76, 97). However, anti-infectives were more commonly reported to be associated with ADR-related admissions in developing countries (23, 28, 42, 66, 156) than developed countries. Top three ADRs commonly reported to cause hospital admissions were gastrointestinal (GI) bleeding (12, 20, 34, 97, 100, 105), electrolyte and metabolic disturbances (9, 16, 23, 58, 94) and cardiovascular disorders (9, 17, 20, 30, 32, 291) (Table 2.1).

2.5.4 Risk factors associated with ADR-related admissions

Thirty studies included in this review have reported risk factors associated with ADR-related hospitalisation of adults, detailed in Table 2.2. These risk factors for hospital admissions have been categorised as patient-related, disease-related, medication-related, and healthcare-related. Eight studies found older age to be an independent predictor for ADR-related admissions (Table 2.2). Five studies reported that female gender was an independent risk factor for ADR-related admissions (9, 20, 94, 97, 169). Increasing medical complexity, both in terms of number of co-morbidities (9, 95) and number of medications (9, 14, 16, 17, 94, 96-98), were reported to be associated with an increased risk for ADR-related hospitalisations. In addition, specific medical conditions such as HIV (23), renal failure (100) and heart failure (9) were also reported to be associated with ADR-related hospital admissions, with HIV identified as a risk factor for ADR-related admission only in developing countries.

Table 2. 2 Identified predictors for ADR-related admissions

Category of predictive risk factors	Identified specific predictors [referenced studies]
Patient-related	Age (15, 20, 39, 55, 98, 99, 103)
	Female gender (9, 20, 94, 97, 169)
Disease-related	Number of comorbidities (9, 95)
	Higher Charlson Comorbidity Index (37)
	Severe ADRs (37)
	Renal failure (100)
	Heart failure (9)
	HIV/AIDS (23)
	Gastrointestinal bleeding (52)
	Hormonal therapy (104)
	History of falls (52)
Medication-related	Number of drugs (9, 14, 16, 34, 94, 96, 97, 107)
	Anticoagulant use (96, 99, 109)
	NSAIDs (109)
	Angiotensin-converting enzyme inhibitors (109)
	Digitalis use (105)
	Antibacterial use (96)
	Antiretroviral drug use (23, 199, 200)
	Self-medication (96)
	Drug interactions (100)
	Alcohol use (9)
Health system-related	Ward type (104)
	Hospital site (163)

Table 2. 3 Comparison of prevalence and proportion of ADR-related hospital admission, severe ADR, preventable ADR and ADR-related mortality in developed and developing countries.

Statistical tests	Prevalence of ADR-related admission (%)		Proportion of severe ADRs (%)		Proportion of preventable ADRs (%)		Proportion of ADR-related mortality (%)	
	Developed country	Developing country	Developed country	Developing country	Developed country	Developing country	Developed country	Developing country
Minimum	0.5	0.2	3.6	4.0	20.0	50.0	0.0	0.5
Maximum	37.5	54.5	62.0	74.5	92.0	85.7	6.7	10.0
Median	6.3	5.5	20.0	10.0	71.7	59.6	1.7	1.8
IQR(Q1,Q3)	7.7(3.3-11.0)	15.8(1.1-16.9)	14.2(9.8-24.0)	18.3(5.7-24.0)	17.7(62.3-80.0)	28.1(51.5-79.6)	4.1(0.7-4.8)	7.2(0.8-8.0)

Note: IQR-Interquartile range, Q1-Lower quartile, Q3-Upper quartile.

2.6 Discussion

Detection of ADR-related hospitalisation provides an important measure of the burden of drug-related morbidity on patients and on the healthcare system and also recognition of drug safety as a major public health priority (56). The findings from this review indicate that ADR-related hospitalisations constitute a substantial healthcare issue for the adult population, regardless of the socioeconomic context of developed or developing countries,.

The overall prevalence of ADR-related hospitalisation ranged from 0.2% to 54.5%, which is comparable with the previous review findings of 0.2% to 41.3% by Beijer *et al.* (285). The median prevalence of this review was also comparable with three other reviews (282, 284, 285). However, there were marked differences in the prevalence of ADR-related hospitalisations between studies selected for this review, possibly reflecting a lack of standardisation across the studies, especially with regard to the definitions of ADR used (24, 283); and causality assessment and detection methods (84, 88).

There is large difference in the prevalence of ADR-related admissions between studies even within the same countries. For instance, in Brazil Noblat *et al.* reported a prevalence of 0.4% ADR-related admissions (66) whereas Varallo *et al.* reported 54.5% (107). Similarly, in the United Kingdom Patel *et al.* reported a prevalence of 0.5% ADR-related admissions (17) whereas Green *et al.* reported 7.5%. The reasons for such large differences in ADR prevalence are likely due to the difference in study designs (higher proportions of prevalence were reported in prospective than retrospective studies in most cases), the population (higher prevalence of ADRs were reported in elderly age groups compared to broader age groups; differences in prescribing of higher or lower risk medications)(295), method of ADR identification (chart review versus patient/staff interview). Moreover, there is no gold standard method of ADR causality assessment, different researchers used different tools such as Naranjo et al. (88) and

WHO (283) causality assessment methods, which influence the prevalence estimates. Additionally, various research groups may have had differing interpretations of the causality assessment criteria. A large prevalence of ADR-related admissions were reported by Budnitz *et al* (290)and McDonnell *et al* (33) from United States despite being retrospectively designed studies; this might be due to high proportions of chronic disease, elderly patients and the high prevalence of medication use in the USA.

Although there was a comparable prevalence of ADR-related hospitalisations between developing and developed countries, there was a wide variation and inconsistent prevalence between studies, especially in developing countries. The reasons for this could be variation in therapeutic options used with regard to differences in disease distribution and population characteristics (9, 14, 23, 100), healthcare systems (104), and ethnic origin (168, 250). In addition, complicated case management with multiple medications mainly in developed countries (9, 14, 94) and difference in study designs, primarily retrospective versus prospective design, (282) may have contributed to the variation in reported prevalence. Moreover, the wide variation could be as a result of differences in the populations being studied (for example, elderly populations had a higher rate than adult patients)(285).

Even though there was variation in the medications associated with ADR-related hospitalisations between developed and developing countries, there were medications common to both settings. These included antithrombotics (16, 35, 93-95, 97), NSAIDs (10, 16, 23, 35, 39, 93, 95, 98), and cardiovascular agents (17, 20, 30, 94, 98, 99). These medications have been associated with number of complications such as GI bleeding (20, 97, 99, 100, 105) and electrolyte and metabolic disturbances (9, 16, 23, 58, 94), which were similar to those reported in previous reviews (56, 285, 286).

In contrast to the developed countries, anti-infectives were commonly reported to be associated with ADR-related hospitalisations in developing countries (23, 28, 42, 66, 156). This was probably because of the difference in the population at risk of ADRs in developing countries, particularly in sub-Saharan Africa, where HIV/AIDS co-infections and cross-fertilisation between other chronic illnesses (273) and infectious diseases are common. In addition, lack of proper legislation and policies for anti-infective use, including for ADR reporting, a large number of substandard and counterfeit products circulating in the markets, a lack of independent drug information centres and the irrational use of drugs (283) could have also contributed to the additional burden of ADR-related hospitalisation compared to the developed countries.

Despite the differences in socioeconomic status of the study participants and study designs, there was significant consistency in some risk factors associated with ADR-related hospitalisations. For instance, female gender was associated with increased risk of ADR-related hospitalisation despite women taking similar medications to men (9, 20, 94, 97, 169). Moreover, a recent study by Rodenburg et al (171) showed that there was a pronounced risk among females taking diuretics, cardiotonic glycosides and coronary vasodilators. Possible reasons for the higher susceptibility of women to ADRs could be due to lower body weight and organ size, more body fat and a lower glomerular filtration rate. In addition, poorer educational opportunities, poorer empowerment and status for women (296) compared to men might have led to poorer management and handling of medications, particularly in the developing world, which might expose women to higher risk than men.

Irrespective of the age and socioeconomics of the patients, the number of medications taken was also a consistently reported risk factor for ADR-related admissions (14, 17). The risk of ADR severity also increased as the number of medications increased (52). Possible reasons for

this could be a greater risk of patient error due to more complicated regimens and also a greater chance of drug-drug and drug-disease interactions.

Advanced age was found to be a risk factor in many studies irrespective of the socioeconomic status of the patients; this is hypothesised to be mainly as a result of increased fragility, medical complexity, disease burden and physiological changes. This is in agreement with a previous review (285). In contrast, Mjorndal et al. (166) and Hellden et al. (167) reported that advancing age itself had no effect on ADR-related hospitalisations, which could alternatively be explained by poor monitoring of renal function and adjustment of pharmacotherapy (drug selection and dose), particularly in very elderly women which can contribute to the occurrence of ADRs.

There was great diversity in the role of specific medical conditions as independent risk factors for ADR-related hospitalisation. This makes it challenging to make firm conclusions on the contribution of specific medical conditions to the risk. Heart failure, renal failure and liver failure were clear risk factors for ADR-related admission (10, 32, 297). Immunosuppression with HIV and highly active antiretroviral therapy (HAART) were revealed as risk factors for ADR-related hospitalisation mainly in developing countries, as reported by Mehta *et al.* (23). Dimie et al. (199) from Nigeria similarly reported that direct HAART-related complications in general and zidovudine-induced severe anaemia requiring blood transfusions in particular, were the most common reason for hospitalisation, and resulted in a six-fold risk of mortality in those with severe anaemia. Moreover, Henry *et al.* from Cameroon (200) reported that zidovudine-related severe anaemia was one of the main reasons for hospitalisations. Thus, patients' HIV positive status tended to increase the risk of experiencing ADRs and mortality when compared with those who were HIV negative or whose HIV status was unknown (23). This represents a special area of focus for practitioners in developing countries.

Severity and preventability of ADRs were under-reported in these studies. The highest proportion of severe cases reported was 62.0% by Hofer-Dueckelmann et al. in Germany (94). The reason for this might be due to frequent use of drugs with narrow therapeutics index, such as anticoagulant and higher medication regimen complexity. The majority of preventable ADRs were known to have occurred in the elderly. Thus, identifying preventable ADRs along with an understanding of the causes such as poor therapeutic monitoring and pharmacotherapeutic adjustments (167), is crucial in constructing interventions to minimise ADR-related admissions. In addition, patient empowerment through health education and literacy may reduce the burden of ADR-related hospital admissions such that complications arising from therapy can be addressed promptly or prevented altogether.

There is large differences in the proportion of preventable ADR-related admissions irrespective of the socioeconomic status of the countries. The reason for huge difference in the proportion of preventable ADR could be lack of gold standard method for assessing preventability of ADR, as there is conflicting evidence on which instruments have the highest reliability for assessing preventability (298). In the articles reviewed we found that reliability was not reported in most of them and when reported, it varied markedly across studies. It was also revealed that intra- and inter-rater reliabilities of the preventability judgments of ADR was poorer when using implicit instruments compared to an explicit instruments (205), perhaps due to the larger impact of the individual reviewers' clinical judgment in implicit instruments. In addition, there is difference in the risk factors and capacity of the health professionals in addressing these risk indicators of ADR. There is also substantial difference between retrospective versus prospective studies – where more data is available to make a judgment in prospective studies.

In the majority of cases, prospective observational studies were associated with a higher median prevalence of ADR-related admissions than retrospective studies. The reason could be, in prospective studies in addition to reviewing the medical records; patients are interviewed, observed and evaluated exhaustively for the presence of ADR. Therefore, there is more chance of identifying any hidden ADRs on top of reviewing physicians' records only as there is more data available at the time of admission compared to retrospective data.

The main strength of this study was the strict inclusion criteria applied regarding ADR-related hospitalisations in the adult population and the focus on comparison of studies from developed and developing countries. In addition, the majority of the studies included a clear description of the method applied in the identification of ADRs, prevalence of ADR-related hospitalisations, severe and preventable ADRs, frequency of drugs causing ADR and risk factors for ADR-related admissions. Risk factors for ADR-related admissions were discussed in a more comprehensive manner than in previous reviews. Moreover, the review was limited to mainly observational studies focussing on ADR-related hospitalisations in adults, in an attempt to minimise the heterogeneity among included studies.

Despite the above strengths, there was a limited number of articles and inconsistent prevalence reporting from developing countries. ADR causality, severity and preventability described in this review were obtained from different studies that used different measurement criteria or scales that might have created discrepancies in the rates reported. In addition, the proportions of ADR-related mortality, severe and preventable reactions were reported in only about half of the studies, and findings are therefore not necessarily generalizable. Moreover, studies conducted in intensive care unit were excluded as our focus was on admissions to general medical wards, which is consistent with many other studies.

2.7 Conclusions

ADRs are an important cause of hospital admission and contribute to substantial morbidity in patients and pressure on the healthcare system. The prevalence of ADR-related hospitalisation and mortality was similar in both the developed and developing worlds and many of the same medication classes were often implicated. The main difference between developed and developing worlds was the influence of HIV/AIDS and other infectious diseases and their associated medications. The prevalence of ADR-related hospitalisation was higher in prospective studies than retrospective studies irrespective of a country's sociodemographic status, suggesting the need for a focus on prospective methodologies for identification and documentation of ADRs during post-marketing surveillance and pharmacovigilance studies.

The majority of ADRs were preventable, highlighting the importance of improving medication use, particularly in vulnerable patient groups, such as the elderly, patients with comorbidities and multiple drugs, and in the developing world, patients with HIV/AIDS.

The proportion of severe ADRs in developed countries were twice that of developing countries indicating that there were a large number of older patients with greater comorbidity and who were likely taking more medications due to both greater age and greater opportunity to obtain a wider variety of medications.

The use of a standardised, simple methodology for assessment of causality, severity, and preventability should be considered which would greatly contribute towards an improved understanding of the global nature and extent of this public health problem and the measures that can be taken to minimise the occurrence of preventable ADR-related admissions.

Chapter Three

3. Predictors of adverse drug reaction-related hospitalisation in Southwest Ethiopia: A prospective cross-sectional study

3.1 Abstract

Background: Adverse drug reactions (ADRs) are an important causes of morbidity and mortality in the healthcare system; however, there are no studies reporting on the magnitude and risk factors associated with ADR-related hospitalisation in Ethiopia.

Objectives: To characterise the reaction types and the drugs implicated in admission to Jimma University Specialized Hospital, Southwest Ethiopia, and to identify risk factors associated with ADR-related hospitalisation.

Methods: A prospective cross-sectional study was conducted from May 2015 to August 2016 among consenting patients aged ≥18 years consecutively admitted to medical wards taking at least one medication prior to admission. ADR-related hospitalisations were determined through expert review of medical records, laboratory tests, patient interviews and physical observation. ADR causality was assessed by the Naranjo algorithm followed by consensus review with internal medicine specialist. ADR preventability was assessed using Schumock and Thornton's criteria. Only definite and probable ADRs that provoked hospitalisation were considered. Binary logistic regression was used to identify independent predictors of ADR-related hospitalisation.

Results: Of 1,001 patients, 103 (10.3%) had ADR-related admissions. Common ADRs responsible for hospitalisation were hepatotoxicity (35, 29.4%) and acute kidney injury (27, 22.7%). The drug classes most frequently implicated were anti-tubercular agents (45, 25.0%) followed by antivirals (22, 12.2%) and diuretics (19, 10.6%). Independent predictors of ADR-

related hospitalisation were body mass index (BMI) <18.5 kg/m^2 (adjusted odd ratio [AOR]=1.69; 95% confidence interval [CI]=1.10-2.62; p=0.047), pre-existing renal disease (AOR=2.84; 95%CI=1.38-5.85, p=0.004), pre-existing liver disease (AOR=2.61; 95%CI=1.38-4.96; p=0.003), number of comorbidities ≥4 (AOR=2.09; 95%CI=1.27-3.44; p=0.004), number of drugs ≥6 (AOR=2.02; 95%CI=1.26-3.25; p=0.004), and history of previous ADRs (AOR=24.27; 95%CI=11.29-52.17; p<0.001). Most ADRs (106, 89.1%) were preventable.

Conclusions: ADRs were a common cause of hospitalisation. The majority of ADRs were preventable, highlighting the need for monitoring and review of patients with lower BMI, ADR history, renal and liver diseases, multiple comorbidities and medications. ADR predictors should be integrated into clinical pathways and pharmacovigilance systems.

Key words: Adverse drug reaction, hospital admission, hospitalisation, Jimma University Specialised Hospital, Southwest Ethiopia

3.2 Introduction

Adverse drug reactions (ADRs) are one of the leading causes of morbidity and mortality in the healthcare system (22). Globally, studies have reported that the overall prevalence of ADR-related hospitalisation varies from 0.2% (28) to 54.5% (29). A recent review of 43 observational studies identified a comparable prevalence of ADR-related hospitalisation in developed and developing countries (22). However, most of the studies included in this review were conducted in developed countries, where the disease characteristics and prevalence, access to medicines, drug use patterns, and management systems differ markedly from those in developing countries (299). With respect to potential risk factors for ADRs, developing countries differ from developed countries in several important areas. These include greater proportions of patients taking anti-tuberculosis (anti-TB) and antiretroviral therapy (ART)

(268), a high prevalence of anaemia and malnutrition (270), widespread use of traditional remedies (269), a higher incidence of concomitant anti-TB drugs and ART with overlapping adverse effects (270), and increasing rates of concomitant infectious and non-communicable diseases demanding multiple medications with potential interactions (23, 199, 200, 273, 274). There are also higher frequencies of genetic variants conferring increased risk for ADRs for commonly used drugs treating cancer, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) and tuberculosis (TB) in persons of African descent (272).

In Ethiopia, a developing country, the risk of ADR-related hospitalisation is a health concern due to an increasing number of patients eligible for anti-TB and ART, due to decentralisation and scale-up of the HIV/AIDS care programme (277), and concomitant drug management of HIV/TB co-infected patients (277). According to a 2014 World Health Organization (WHO) report, the prevalence of all forms of TB was 211 per 100,000 of the population, of whom 13% of patients were HIV co-infected (300). The prevalence of HIV among the adult population in 2015 was estimated to be 1.0% with national ART coverage of 52.0% (301). There is growing attention to chronic disease management with multiple medications (273, 302). The use of new and complex therapies for chronic diseases has increased due to the establishment of community care programs (303) and strengthening of health systems for chronic care at the level of local health centres, primary, general, and specialised hospitals (303). The provision of primary health care services by health extension workers (health professionals working at the lowest health care level targeting preventive and curative health services at the household level) (278) and the expansion of community pharmacies and drug stores at the community level has remarkably increased medication access and use in the community, although medication regulation is poor (304). There are also higher rates of drug-related problems (305) and irrational use of medicines (306) among patients with chronic illnesses in ambulatory care clinics that could lead to drug-related harm.

Studies have identified several factors contributing to ADR-related hospitalisations including older age (98, 99), female gender (97, 169), increased number of co-morbidities (9, 95), increased number of medications (17), renal diseases (100, 307), liver diseases (308), heart failure (9), higher Charlson Comorbidity Index (CCI) (37), presence of chronic illnesses (16, 176), and history of previous ADRs (14, 33). HIV/AIDS patients taking ART have been identified as a risk factor for ADR-related hospitalisations only in developing countries (23, 101). Drugs commonly reported as contributing to ADRs include anticoagulants (96, 99), non-steroidal anti-inflammatory drugs (NSAIDs) (109), and angiotensin-converting enzyme inhibitors (109). However, studies focussing on risk factors for ADR-related hospitalisation in developing countries are very limited in number (22). Therefore, identification and reporting of factors contributing to ADR-related hospitalisation for community-based patients is crucial to develop preventive strategies to decrease the burden in the developing world (199, 200).

To our knowledge, there are no studies reporting on the prevalence and risk factors associated with ADR-related hospitalisation in Ethiopian patients. Thus, the main aim of this study was to characterise the reaction types and the drugs implicated in admission to Jimma University Specialized Hospital (JUSH), Southwest Ethiopia, and to identify risk factors associated with ADR-related hospitalisation.

3.3 Methods

3.3.1 Study setting, design and population

This study was conducted at the JUSH, which is the major public hospital in southwest Ethiopia with a catchment population of about 15 million people (258).

A prospective cross-sectional study was conducted from May 2015 to August 2016. Consenting patients with complete medical records aged ≥18 years and taking at least one medication prior

to admission to medical wards were included in the study. Patients were excluded if they were unwilling to participate, unable to be interviewed due to health or other reasons, not taking at least one medication prior to admission and had incomplete medical and medication records.

3.3.2 Data collection

One of the authors (MTA) interviewed consecutively admitted patients as soon as practical for socio-demographic information, social drug use, medical history, drug allergies, use of over-the-counter and herbal medicines (S1 Table). Patients' medical records were reviewed for admission diagnosis, ADR history, and clinical data within 48 hours of admission. Medication exposure in the month preceding hospitalisation was obtained through review of patients' medical records and /or interview with the patient or family members. Common laboratory tests were evaluated within 48 hours of admission for each patient case including: renal function (serum creatinine mg/dL, blood urea nitrogen mg/dL and estimated glomerular filtration rate (eGFR) mL/min/1.73m^2), liver function (alanine transaminase IU/L, aspartate transaminase IU/L, alkaline phosphatase IU/L and total bilirubin mg/dL), and complete blood count (white blood cell count cells/mm^3, red blood cell count cells/mm^3, haemoglobin g/dL, haematocrit %, and platelet count cells/mm^3). Parameters describing nutritional and metabolic status (serum albumin g/dL, total triglyceride mg/dL, low-density lipoprotein mg/dL, high-density lipoprotein mg/dL, glucose mg/dL), serum electrolytes (serum calcium mmol/L, potassium mmol/L, and sodium mmol/L), and coagulation status (prothrombin time) were recorded. Vital statistics such as body temperature, blood pressure, respiratory rate, and pulse rate were recorded at admission. Other diagnostic data, such as echocardiography, ultrasound, electrocardiogram, and viral markers and urinalysis results were also evaluated.

3.3.3 Definitions of terms and variables used

The WHO definition of an ADR was used in this study: "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" (21). This definition excludes treatment failure, drug abuse, intentional drug overdose, and accidental or self-poisoning. Alcohol consumption was recorded as number of standard drinks per day. Khat chewing, which was of interest as it contributes to elevated blood pressure (309), was defined as regular chewer if a patient chewed khat at least four times per week. Drugs were classified using the WHO Anatomical Therapeutic Chemical Classification (ATC) System (310) and diagnoses were coded according to International Classification of Primary Care 2nd edition (311). Calculation of the number of medications was based on the number of active ingredients in single and combination products (312). A cut off point for polypharmacy was ≥6 medications (313). A cut off point for comorbidities was ≥4 diseases based on a similar study (101). Adult nutritional status was assessed using the body mass index (BMI) (314) and classified as <18.5 kg/m^2 and ≥ 18.5 kg/m^2 for analysis purposes. Patients were considered to have pre-existing chronic kidney disease if the eGFR was <60 mL/minute/1.73m^2 and they had a documented abnormal renal ultrasound (abnormal renal echogenicity or kidney size or presence of cysts) for at least 3 months prior to admission (315). Drug-induced acute kidney injury was suspected among patients with baseline renal insufficiency (eGFR < 60 mL/minute/1.73m^2), volume depletion, and multiple exposures to nephrotoxic agents prior to admission, as long as other potential causes were excluded. Chronic liver disease was considered pre-existing if liver diseases (such as cirrhosis, chronic viral hepatitis) or liver dysfunction or liver injury were documented by the treating physician prior to admission (308). Drug-induced hepatotoxicity was suspected when aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels were 3 or more times the upper normal limit (UNL) or total bilirubin was 2 or more times

UNL (316), as long as other potential causes were excluded. The response to rechallenge or re-exposure to some drugs, such as anti-TB drugs, were implemented based on the WHO guidelines for the treatment of TB (317). HIV/AIDS and TB patients were those patients diagnosed with HIV/AIDS and TB, respectively, and taking ART and anti-TB drugs prior to the current admission. All comorbidities were defined as present if documented in the medical records. A patient who had studied at least to a primary school level and was able to read and write in the local language(s) was considered as educated, whereas other patients were considered uneducated. According to the Ethiopian context, cities and small towns were considered as urban areas while rural villages or other similar clusters were considered as rural areas. The readmitted cases were treated as separate cases as far as the reasons for readmissions were different from the previous cause of admissions.

3.3.4 Identifying ADR-related hospitalisation

The primary researcher (MTA) evaluated all patients admitted to medical wards during the study period to assess if the admission had been caused by an ADR. The identification of whether one or more drugs led to the hospitalisation was based on a review of medical records, evaluation of laboratory tests, interview with patients or family members about medication usage and physical observation. An ADR was suspected if there was a relationship between the time of drug administration and the onset and course of the adverse reaction, while excluding other potential causes. The known adverse reaction profile of each drug was evaluated based on Ethiopian National Drug Formulary (2014), British National Formulary (318), and Up-To-Date 19.3 (319). Confirmation of the causal relationship of an ADR to the suspected medication was performed using the Naranjo ADR assessment scale (88). Applying the Naranjo algorithm, ADRs were classified as definite (9-12 points), probable (5-8 points), possible (1-4 points), or doubtful (0 points). The senior supervising internal medicine specialist

(DY) independently and blindly reviewed all cases of suspected ADRs and cases without suspected ADRs for the presence of ADRs and to confirm the Naranjo rating using a similar approach to other studies (116, 213). The primary researcher (MTA) and the senior supervising internal medicine specialist met to reach a consensus decision on the presence of an ADR-related admission and excluded possible and doubtful cases. When consensus was not reached on the causality assessment, an additional clinical pharmacy specialist's opinion was sought for majority decision. Only definite and probable ADRs that provoked hospitalisation were considered. ADRs were assessed for preventability using Schumock and Thornton criteria (201) through the same approach. ADRs were classified as type A (dose dependent, augmented pharmacological and predictable reactions) and type B (bizarre, dose independent and non-predictable reactions) according to the Rawlins and Thompson classification method (75). ADRs observed during the hospital stay were excluded.

3.3.5 Data analysis and interpretation

Data was recorded into an Access database (2016, Microsoft, Redmond, Washington) and analysed using the IBM Statistical Package for the Social Science (IBM SPSS version 23.0 Inc., Chicago, Illinois). Frequency of adverse reaction types and drugs implicated were determined. The chi-square test or Fisher's exact test were used to compare categorical data between ADR- and non-ADR patients. For non-normally distributed variables, comparisons were undertaken with Mann-Whitney tests and the results were presented as medians and interquartile ranges (IQR). For normally distributed continuous variables, comparisons were performed using Student's t-tests with results presented as means and standard deviations (SD).

Independent variables were assessed for multicollinearity and association to rule out correlation between two or more independent variables using variance inflation factor. Independent variables with $p<0.25$ in univariate analyses were entered into a multivariable binary logistic regression model to determine independent predictors of ADR-related hospitalisation. The

performance of the ADR-related admission risk prediction model was assessed using the area under the receiver operator curve (AUROC), which assesses the ability of independent risk score to predict ADR-related admissions. The ROC curve was prepared using R (2015, R Foundation for Statistical Computing, Vienna) (320). A p value of <0.05 was considered statistically significant in all analyses.

3.3.6 Ethics

The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (reference number H0014718) and the Jimma University Institutional Review Board (reference number RPGC/58/2015). We received permission from Jimma University Specialised Hospital management to conduct the research. Written informed consent was obtained from all individual participants included in the study.

3.4 Results

3.4.1 General information

A total of 3,224 patients were screened; 2,223 patients were excluded due to age <18 years (255), not taking at least one medication prior to admission (576), incomplete medical and medication records (70), unwillingness to participate (463) and inability to be interviewed as a result of health or other reasons (859). One thousand one patients fulfilled the inclusion criteria. Therefore, ADR-related admissions were estimated to be 3.4% (103/3,224) of all medical admissions and 10.3% (103/1,001) of the patients who met the inclusion criteria during the study period (Fig 3.1).

One hundred and nineteen ADRs were identified among the 103 patients, equating to 1.2 ADRs per patient. Of these, 26.1% were definite and 73.9% were probable. Most ADRs (106, 89.1%) were considered preventable. Ninety-nine (83.2%) of the ADRs were considered pharmacologically predictable (type-A reactions) (Table 3.1).

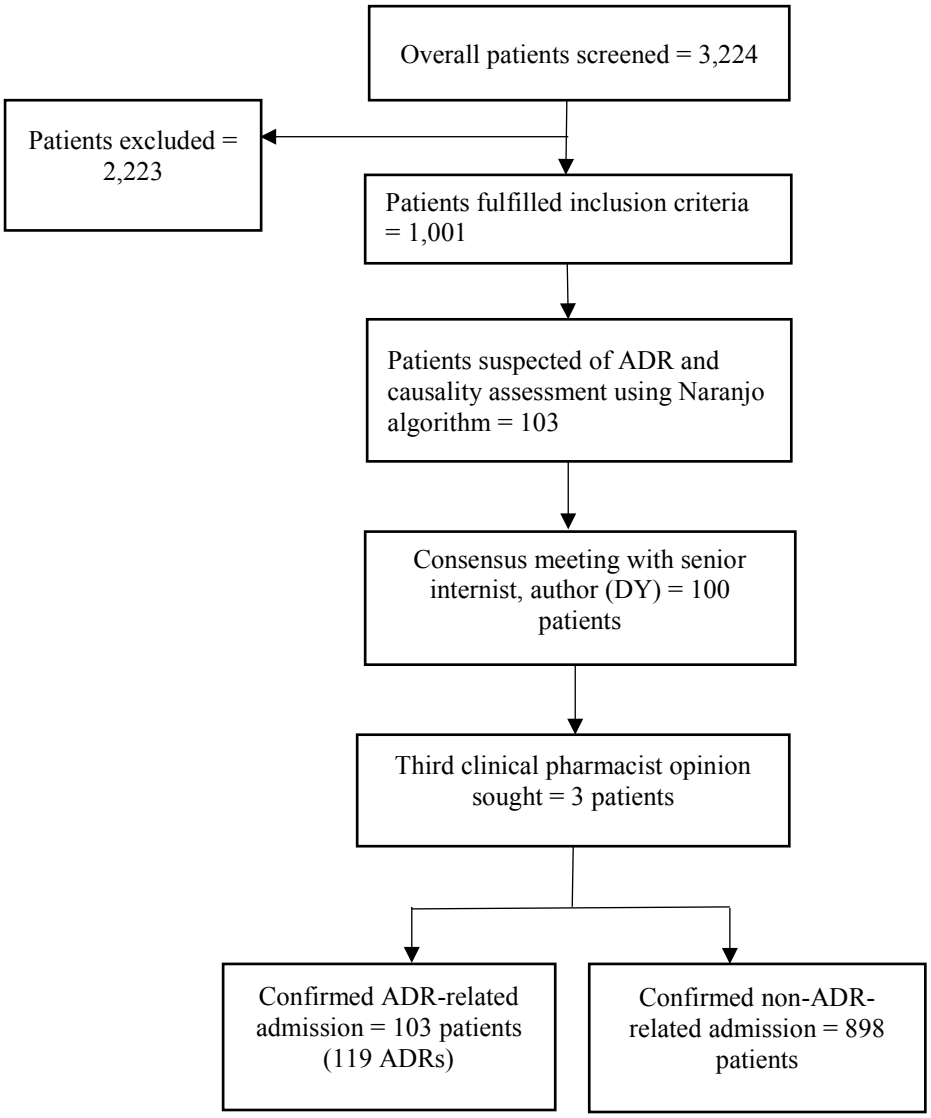


Figure 3. 1 Flow diagram of ADR assessment procedure

Table 3. 1 Causality, type and preventability of ADRs causing hospitalisation (N=119)

ADR classifications	n (%)
Causality of ADRs	
Definite	31(26.1)
Probable	88 (73.9)
Preventability scale	
Not preventable	13 (10.9)
Definitely preventable	19 (16.0)
Probably preventable	87 (73.1)
Rawlins classification of reaction	
Type A (pharmacologically predictable)	99 (83.2)
Type B (pharmacologically non-predictable)	20 (16.8)

3.4.2 ADR characteristics and drugs implicated in ADRs

The most common ADRs responsible for hospital admissions were hepatotoxicity (35, 29.4%) followed by acute kidney injury (due to drug-induced pre-renal azotaemia and nephrotoxicity) (27, 22.7%), skin reactions (8, 6.7%), hypokalaemia (7, 5.9%), and gastrointestinal bleeding or gastritis (7, 5.9%). Commonly implicated drugs in hepatotoxicity were isoniazid (21, 11.7%) followed by pyrazinamide (18, 10.0%), efavirenz (5, 2.8%), and atorvastatin (5, 2.8%). Commonly implicated drugs in acute kidney injury were tenofovir (9, 5.0%), furosemide (7, 3.9%), and enalapril (7, 3.9%). The drugs most commonly suspected of causing skin reactions were sulfamethoxazole (2, 1.1%), trimethoprim (2, 1.1%) and rifampicin (2, 1.1%). The drug most commonly suspected of causing hypokalaemia was furosemide (6, 3.3%). The drugs most commonly suspected of causing gastrointestinal bleeding were warfarin (3, 1.7%), heparin (3,

1.7%), and diclofenac (3, 1.7%). In general, anti-TB agents constituted the major source of ADRs (45, 25.0%) followed by antivirals (22, 12.2%) and diuretics (19, 10.6%). Table 3.2 provides a summary of ADRs and causative agents.

Table 3. 2 ADRs (N=119) and implicated drugs (N=180)

ADR types	n (%)	Drugs implicated in causing ADRs (n)	n (%)
Hepatotoxicity (cholestatic (22), hepatocellular (8), and mixed (5))	35 (29.4)	Isoniazid (21), pyrazinamide (18), atorvastatin (5), efavirenz (5), acetyl salicylic acid (ASA)[#] (2), clopidogrel (2), propylthiouracil (2), paracetamol (2), phenytoin (2), rifampicin (1), omeprazole (1), ritonavir (1), atazanavir (1)	63 (35.0)
Acute kidney injury (27)	27 (22.9)	Tenofovir (9), furosemide (7), enalapril (7), diclofenac (4), acetyl salicylic acid[#] (4), cimetidine (1), heparin (1), clopidogrel (1)	34 (18.9)
Skin reactions involving mucous membrane (pruritic skin rash (6), gingival hyperplasia (1) and Steven Johnson Syndrome(1))	8 (6.7)	Sulfamethoxazole (2), rifampicin (2), trimethoprim (2), ciprofloxacin[*] (1), ampicillin (1), isoniazid (1), nevirapine (1), methotrexate (1), cloxacillin (1), phenytoin (1), phenobarbital (1), warfarin (1)	15 (8.3)
Gastrointestinal bleeding (6) and gastritis (1)	7 (5.9)	Warfarin (3), heparin (3), diclofenac (3), clopidogrel (2), acetylsalicylic acid[#] (2), propylthiouracil (1), glibenclamide (1)	15 (8.3)
Hypokalaemia	7 (5.9)	Furosemide (6), insulin (3), digoxin (1)	10 (5.6)
Hypocalcaemia	6 (5.0)	Furosemide (6)	6 (3.3)
Diarrhoea	5 (4.2)	Lamivudine (3), rifampicin (2), amitriptyline (1)	6 (3.3)
Hypoglycaemia	4 (3.4)	Insulin (4), glibenclamide (1), acetyl salicylic acid (1)	6 (3.3)
Anaemia	4 (3.4)	Sulfamethoxazole (2), trimethoprim (2), methotrexate (1), phenytoin (1)	6 (3.3)
Swelling of tongue (angioedema) (2) and severe dry cough (1)	3 (2.5)	Enalapril (3)	3 (1.7)
Delirium	2 (1.7)	Efavirenz (2)	2 (1.1)
Thrombocytopenia	2 (1.7)	Isoniazid (1), heparin (2)	3 (1.7)
Falls	1 (0.8)	Diazepam (1), thioridazine (1)	2 (1.1)
Osteomalacia	1 (0.8)	Phenobarbital (1), phenytoin (1)	2 (1.1)
Hypotension (orthostatic)	1 (0.8)	Atenolol (1)	1 (0.6)
Syncope	1 (0.8)	Metoprolol (1)	1 (0.6)
Dizziness	1 (0.8)	Quinine (1)	1 (0.6)
Blurred vision	1 (0.8)	Amlodipine (1)	1 (0.6)
Vertigo	1 (0.8)	Metoprolol (1)	1 (0.6)
Lactic acidosis	1 (0.8)	Metformin (1)	1 (0.6)
Vaginal bleeding	1 (0.8)	Medroxyprogesterone acetate (1)	1 (0.6)

[^]suspected to have caused lactic acidosis, [*] suspected to have caused Steven Johnson Syndrome, [#]high dose (≥300mg) acetyl salicylic acid

3.4.3 Drugs used

Out of the 4,018 drugs used by the 1,001 patients, 562 (14.0%) were used by patients who experienced ADR-related admissions. One-hundred and eighty of the 562 drugs were

implicated in the 119 ADRs. Anti-infectives constituted the major proportion (52.1% versus 40.5%, p=0.001) followed by cardiovascular system agents (18.9% versus 24.9%, p=0.013) in both the ADR and non-ADR groups, respectively (Table 3.3).

Table 3. 3 Comparison of drugs used between non-ADR and ADR patient groups

ATC class name	Non-ADR group n (%)	ADR group n (%)	p-value
Alimentary tract and metabolism	348 (10.1)	57 (10.1)	0.962
Blood and blood forming organs	374 (10.8)	46 (8.1)	0.085
Cardiovascular system	862 (24.9)	106 (18.9)	0.013
Dermatologicals	4 (0.1)	2 (0.4)	0.173
Genitourinary system and sex hormones	19 (0.5)	2 (0.4)	0.556
Systemic hormonal preparations	96 (2.8)	9 (1.6)	0.113
Anti-infective for systemic use	1398 (40.5)	293 (52.1)	0.001
Antineoplastic and immunomodulating agents	0 (0.0)	1 (0.2)	NA[a]
Musculoskeletal system	78 (2.3)	9 (1.6)	0.331
Nervous system	188 (5.4)	24 (4.3)	0.273
Anti-parasitic products	37 (1.1)	6 (1.1)	0.995
Respiratory system	52 (1.5)	7 (1.2)	0.640
Total	3456 (100.0)	562 (100.0)	

[a]NA = Not applicable, ATC = Anatomical Therapeutic Chemical Classification

3.4.4 Patient characteristics in univariate analysis

The main socio-demographic difference between the ADR-and non-ADR groups was a difference in urban versus rural residence (P=0.004), where urban residents were more likely to be admitted with ADRs than rural residents. The mean body mass index (kg/m^2) was lower in the ADR group, 19.1±2.8 versus 20.1±2.9, p=0.004. There was no difference between the ADR and non-ADR groups for age, gender, educational status, smoking, alcohol use, khat chewing, and herbal use. Patients with a previous ADR history (p<0.001), pre-existing renal diseases (p=0.003), pre-existing liver diseases (p<0.001), TB taking anti-TB drugs (p<0.001),

and HIV/AIDS taking ART ($p<0.001$) were more likely to be admitted with ADRs than those without these risk factors. Similarly, ADR admission was more likely in patients who had been hospitalised in the preceding 3 months ($p=0.030$). Patients in the ADR group had a more comorbidities (4.0 ± 1.4 versus 3.2 ± 1.2, $p<0.001$) and used more drugs than the non-ADR group (5.5 ± 2.7 versus 3.9 ± 2.1, $p<0.001$) (Table 3.4).

Table 3. 4 Characteristics of patients experiencing ADR-related admissions and non-ADR-related admissions at Jimma Universality Specialised Hospital

Risk factors	Non-ADR related admissions	ADR-related admission	p-value
Total patients	N=898	N=103	
Age, median (IQR)	40 (28-55)	40 (28-60)	0.490
Gender, female n (%)	404 (45.0)	51 (49.5)	0.382
Body mass index (kg/m^2), mean ± SD	20.1±2.9	19.1±2.8	0.004
BMI (kg/m^2), n (%)			
<18.5kg/m^2	260 (29.0)	44 (42.7)	
>/=18.5 kg/m^2	638 (71.0)	59 (57.3)	0.004
Education, n (%)			
Educated	613 (68.3)	68(66.0)	
Uneducated	285 (31.7)	35(34.0)	0.644
Residence, n (%)			
Urban resident	421 (46.9)	64 (62.1)	
Rural resident	477 (53.1)	39 (37.9)	0.003
Alcohol users, n (%)	218 (24.3)	17 (16.5)	0.080
Khat chewers, n (%)	121 (13.5)	5 (5.9)	0.141
Herbal users, n (%)	73 (8.1)	6 (5.8)	0.710
Previous ADR history, n (%)	12 (1.3)	29 (28.2)	<0.001
eGFR, n (%)			
<60 mL/minute/1.73m^2	307 (34.2)	27 (26.2)	
≥60 mL/minute/1.73m^2	376 (41.9)	61 (59.2)	
Unknown	215 (23.9)	15 (14.6)	0.003
Pre-existing renal diseases, n (%)	48 (5.3)	13 (12.6)	0.003
Pre-existing liver diseases, n (%)	70 (7.8)	20 (19.4)	<0.001
Pre-existing heart failure, n (%)	232 (25.8)	27 (26.2)	0.934
HIV/AIDS patients taking ART, n (%)	86 (9.6)	22 (21.2)	<0.001
TB patients taking anti-TB drugs, n (%)	171 (19.0)	36 (35.0)	<0.001
Malignancy of any type, n (%)	40 (4.5)	5 (4.9)	0.853
Cerebrovascular diseases, n (%)	84 (9.4)	4 (3.9)	0.063
Diabetes with complications, n (%)	69 (7.7)	9 (8.7)	0.705
Chronic obstructive pulmonary diseases, n (%)	54 (6.0)	3 (2.9)	0.198
Peptic Ulcer Diseases, n (%)	20 (2.2)	3 (2.9)	0.660
Pre-existing hypertension, n (%)	109 (12.1)	11 (10.7)	0.666
Number of comorbidities, mean ± SD	3.2±1.2	4.1±1.4	<0.001
Number of comorbidities, n (%)			
1-3 comorbidities	563 (62.7)	36 (35.0)	
≥ 4 comorbidities	335 (37.3)	67 (65.0)	<0.001
Number of total medications, mean ± SD	3.9±2.1	5.6±2.7	<0.001
Number of medications, n (%)			
1-5 medications	721 (80.3)	59 (57.3)	
≥ 6 medications	177 (19.7)	44 (42.7)	<0.001
Admission in the preceding 3 months (≥1 admission(s)), n (%)	114 (12.7)	21 (20.4)	0.030

3.4.5 Factors associated with ADR-related admissions

Variables included in the multivariable binary logistic regression model were those with p<0.25 in the univariate analyses. There was no multicollinearity identified in the included variables. Six risk factors associated with ADR-related hospitalisation were identified in the multivariable binary logistic regression model: BMI < 18.5kg/m^2, pre-existing renal diseases, pre-existing liver diseases, number of diagnoses ≥4, number of medications ≥6, and previous ADR history (Table 3.5). The ADR-related admission risk prediction model was found to have an AUROC of 79.0% (95% CI 73.9%-84.1%). The model had a sensitivity of 59.2% and specificity of 86.6%, suggesting that the ADR risk predictors are strong in identifying patients who are not at risk of ADRs and moderate in strength in identifying patients at risk of ADRs (Fig 3.2).

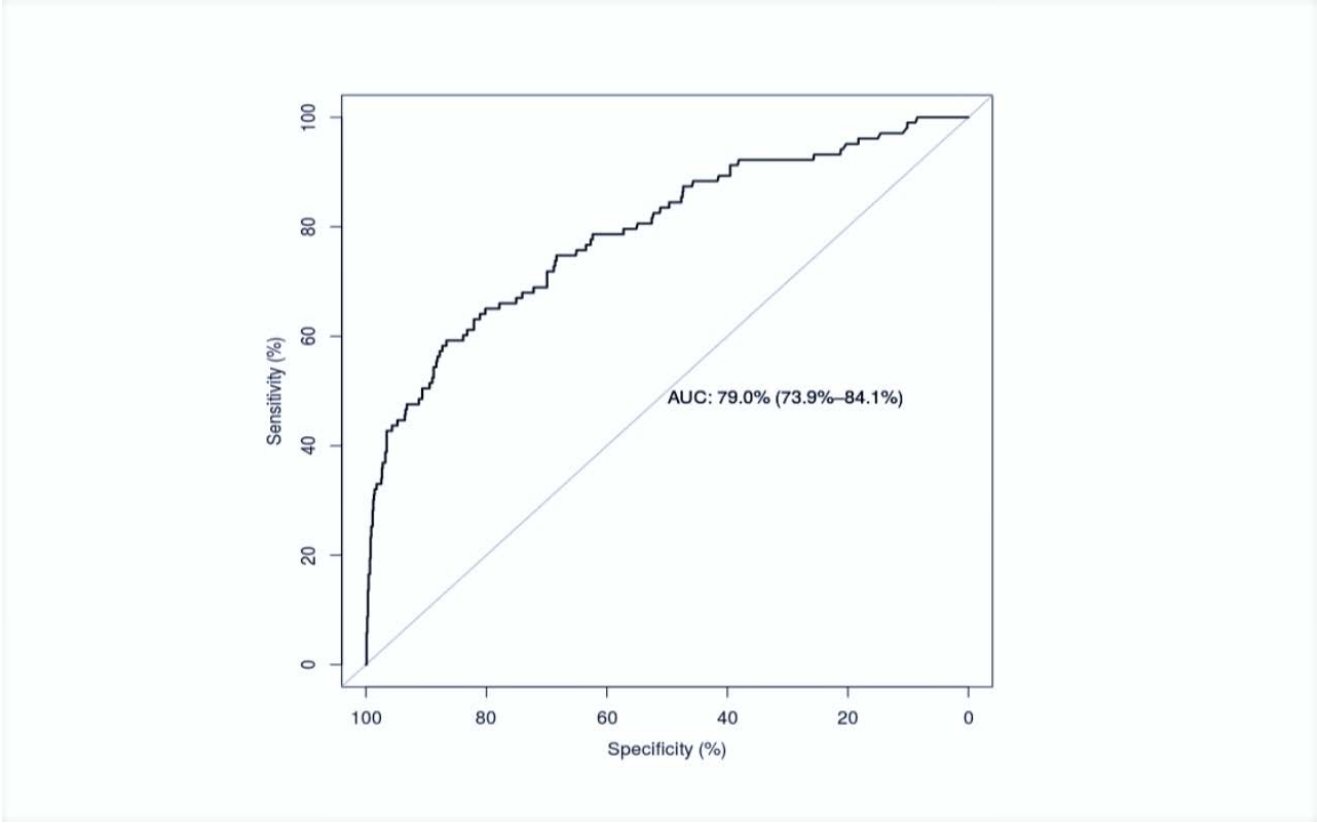


Figure 3. 2 The area under the receiver operator curve showing risk prediction capacity of predicors of ADR-related admission

Table 3. 5 Regression model of ADR-related hospitalisation (N=1,001)

Predictors	Crude		Adjusted	
	OR (95%CI)	p-value	OR (95%CI)	p-value
BMI < 18.5kg/m^2	1.83 (1.21-2.78)	0.004	1.69 (1.10-2.62)	0.047
Pre-existing renal diseases	2.56 (1.34-4.90)	0.005	2.84 (1.38-5.85)	0.004
Pre-existing liver diseases	2.85 (1.65-4.92)	<0.001	2.61 (1.38-4.96)	0.003
Number of comorbidities ≥ 4	3.13 (2.04-4.79)	<0.001	2.09 (1.27-3.44)	0.004
Number of medications ≥ 6	3.04 (1.99-4.64)	<0.001	2.02 (1.26-3.25)	0.004
History of previous ADR	28.94 (14.18-59.05)	<0.001	24.27 (11.29-52.17)	<0.001
Alcohol users	1.62 (0.94-2.79)	0.080	2.45 (1.29-4.65)	0.060
Urban residence	1.86 (1.22-2.83)	0.004	1.50 (0.89-2.52)	0.123
Khat chewers	1.46 (0.88-2.41)	0.141	1.03 (0.58-1.82)	0.932
TB patients taking anti-TB drugs	2.28 (1.47-3.54)	<0.001	1.41 (0.79-2.50)	0.241
HIV/AIDS patients taking ART	4.06 (2.49-6.62)	<0.001	1.33 (0.67-2.65)	0.416
Admission in the preceding 3 months	1.76 (1.05-2.96)	0.030	0.99 (0.51-1.91)	0.965

3.5 Discussion

Identification and reporting of predictors of ADR-related hospitalisation for community-based patients is crucial to develop preventive strategies and responsible care of patients. Medical practitioners may lack awareness of factors predicting ADRs leading to hospitalisation (251, 252). To overcome this, studies, mainly from developed countries (9, 14), have identified several predictors of ADRs causing hospitalisation. However, Ethiopia is a developing country with different healthcare issues. These issues include a lesser ability to provide healthcare (278), a rising proportion of colliding epidemics of infectious and non-communicable diseases demanding multiple medications with potential of interactions (273, 321), a greater prevalence of HIV/AIDS and TB co-infection (322) with overlapping adverse effects of their medications (270), and a less health-literate population (277). Additionally, malnutrition and anaemia are more common than in developed countries (279, 280). Our study, the first in Ethiopia, identified risk factors associated with ADRs, and characterised the reaction types and drugs implicated in admission to the JUSH in Southwest Ethiopia.

We found that 10.3% of admissions were related to ADRs, a prevalence comparable to other studies from South Africa (101) and Argentina (35). Similarly, a review of studies with a similar design to ours found comparable rates of ADRs in both developed and developing countries (22). More than half of the ADR-related admissions were due to hepatotoxicity (mainly due to isoniazid and pyrazinamide) and acute kidney injury (mainly due to tenofovir, enalapril and furosemide). Very few studies, only Patel *et al*. (34) from India and Mouton *et al*. (101) from South Africa, have reported comparable proportions of anti-TB-induced hepatotoxicity and tenofovir-induced renal impairment. The higher prevalence of hepatotoxicity in the current study could be due to concomitant anti-TB, ART and other medications with overlapping hepatotoxic effects. In addition, there was a substantial number of patients with malnutrition in the current study, and potentially the slow acetylation status of

some Ethiopian patients with isoniazid (271) could have exacerbated the hepatotoxic reactions. ADRs commonly responsible for hospitalisation in previous studies included gastrointestinal bleeding (97, 100), electrolyte and metabolic disturbances (9, 16, 23), and cardiovascular disorders (9, 17). Similar ADRs were reported in the current study, but at lower rates probably due to differences in population, diseases characteristics, and drug therapy used.

Most of the predictors of ADRs, such as number of comorbidities (9, 95), number of drugs (9, 16), pre-existing renal failure (100, 323), pre-existing liver diseases (14) and history of previous ADRs (14, 33), were in line with reported findings from both developed and developing countries. HIV/AIDS patients taking ART was identified as an independent predictor that raised the risk of experiencing ADRs in South African studies (23, 101) in 2005 and 2013, respectively. However, this variable was not included in the predictive model in the current study. This is possibly due to the intrinsic relationships between HIV/AIDS and malnutrition, multiple comorbidities, and polypharmacy; although, multicollinearity was not detected. In addition, the strength of the effect of HIV/AIDS patients taking ART as an independent variable is likely less than that of the other variables possibly because HIV/AIDS patients taking ART would have shown crossover-interaction with ADR-related hospitalisation. Additionally, compared to earlier South African studies, the burden of HIV/AIDS is now markedly reduced due to improvements in health care and greater availability of more tolerable ART. The two South African studies were conducted in communities with a high prevalence of HIV/AIDS, when more toxic antiretroviral drugs were in use. Finally, pharmacogenomic variations and other clinical characteristics of patients may have contributed to this difference (271).

Patients with pre-existing renal diseases were more likely to be hospitalised with ADRs than patients with normal renal function, as has been identified in other studies (186, 187). About one-third of the patients presented to JUSH with an eGFR <60 mL/min/1.73m^2 (Table 4), of

whom, 18.5% had pre-existing renal diseases. Nearly one-third of patients were underweight (Table 3.4) and patients with lower BMI were at increased risk of developing ADRs in the current study (Table 3.5), which is in line with another study (162). The combined effect of reduced muscle mass (malnutrition) with chronic illnesses may have contributed to a depressed eGFR despite normal serum creatinine levels, and concealed renal insufficiency may impact on the clearance of hydrophilic drugs (324). In addition, patients in the current study might unintentionally be overdosed based on their weight and/or renal function (using eGFR) that may have led them to develop ADRs. It is therefore important to evaluate renal function to assess the potential therapeutic benefit against the risk of ADRs before initiating renally cleared drugs.

Similar to previous studies (308, 325), patients with pre-existing liver diseases were more likely to develop ADRs. Patients with liver diseases may have multiple comorbidities that require complex medical regimens (326). Pharmacokinetic and pharmacodynamic changes such as a decreased drug elimination or increased toxic metabolites, alteration in drug distribution or protein binding provide opportunity for adverse reactions (308). In addition, some drugs (such as anti-TB and ART) commonly used in the sample population are more likely to be associated with hepatotoxicity, in contrast to drugs used in developed countries.

We found that ADR patients were prescribed a higher number of medications compared to non-ADR patients. That means, increasing medical complexity, both the number of co-morbidities and number of medications, were associated with an increased risk for ADR-related hospitalisations. This is clearly described in the literature (9, 14, 17).

Patients with a previous ADR history were more likely to be admitted with ADRs which is consistent with other studies (14, 33). This might be explained by immunological reactions tending to become worse on repeated exposure due to immunologic memory or cross-reaction to alternative drugs, or because no alternative drugs are available more toxic alternatives must

be used. Most of the ADRs observed were preventable. Most of the ADRs in the current study occurred due to lack of close review of patients' previous clinical and medication-related progress. ADR prevention could have been improved with better knowledge of patients' medical and medication history and associated risk factors.

The ADR-related hospitalisation risk prediction model demonstrated a capacity of 79.0% to discriminate patients who are at risk of ADR-related hospitalisation and those patients who are not. The sensitivity and specificity of the ADR-risk prediction model was 59.2% and 86.6%, respectively, which suggests that it can moderately rule-in patients at risk of ADRs and strongly rule-out those patients not at risk of ADRs. To our knowledge, there is no previously developed similar ADR-risk prediction model in similar study populations aged ⩾18 years, especially in low and middle-income countries. Previous models developed by Zopf et al. (14) and Parameswaran et al. (213) showed comparable results (predictive abilities of 80.0% and 70.0%, respectively), but these models were developed in different populations with different clinical characteristics and drug therapy. Our model was further augmented by an ADR preventability assessment using Schumock and Thornton's preventability assessment criteria, in which the majority of the ADRs were preventable provided these risk factors were reviewed and monitored closely. Although our ADR risk prediction model was not validated in other populations, the majority of the variables identified as independent predictors of ADRs have been described in previous studies (14, 213), suggesting that it is a useful model to assist healthcare practitioners to moderately identify patients at risk for ADRs for implementation of intervention strategies.

Limitations and strengths

Due to the cross-sectional nature of this study, we were only able to consider the incidence of ADRs at a time, so there is a need for future longitudinal studies to consider the incidence of initial and repeat events, and interventional strategies to identify root causes and reduce ADR-

related burdens. The self-reported responses for previous ADR history, for instance, may be limited by recall bias and could have influenced the identified predictors of ADRs, especially in patients taking multiple medications for chronic illnesses. Some questions in the Naranjo causality assessment tool were designed for controlled clinical trials; they were not feasible nor ethical for clinical practice, such as observing effects on giving placebo. Commonly used over-the-counter medicines, contraceptives, topical agents, and herbal remedies were not typically recorded in drug histories, which may have resulted in underestimation of the rate of ADR-related admissions. Some patients who were too ill to be interviewed due to health or other reasons were excluded from the study. This may have resulted in underrepresentation of certain ADRs. The results of this study should be extrapolated to other countries with caution, as the study findings depend on the patient characteristics, disease distribution, healthcare infrastructure, detection methods and definitions of ADRs adopted.

The strength of our study is the prospective identification of ADRs immediately upon admission, allowing for accurate evaluation of the clinical presentation and laboratory parameters. We used a three-step process in ADR assessment, evaluating individual patient's clinical and laboratory parameters, causality assessment using the Naranjo algorithm followed by consensus review with a senior supervising internist, to help mitigate the subjectivity associated with interpretation of some ADRs. Our study is the first to identify independent predictors of ADR-related hospitalisation in Ethiopian patients. Our yearlong sampling avoided the bias associated with anti-infective use pattern due to seasonal variation. Our study was conducted in a teaching and referral hospital serving a population of 15 million; therefore, our results allow extrapolation to other settings in the southwest of Ethiopia.

3.6 Conclusions

ADRs were a common cause of hospitalisation in adults admitted to medical wards of the JUSH. The majority of ADRs were preventable, highlighting the need for close monitoring and review

of patients with lower BMI, previous ADR history, pre-existing renal and liver diseases, multiple comorbidities and medications. The ADR-related hospitalisation risk prediction model demonstrated some ability to identify patients at higher risk for ADRs, and clearly identify patients at lower risk of ADRs. ADR predictors should be integrated into clinical pathways and pharmacovigilance systems. However, validation and refinement of the model is necessary prior to its implementation in routine clinical practice. The prevention of incident ADR may be of paramount importance, as previous ADR was a strong predictor of subsequent events in this patient population. Assessment of ADR causality and effective use of a pharmacovigilance system to monitor drug response in patients should be considered at ambulatory care units of all health care levels to minimise the burden of admissions related to ADRs by targeting the occurrence of preventable reactions.

Chapter Four

4. Mortality from adverse drug reaction-related hospitalisations in southwest Ethiopia: A cross-sectional study

4.1 Summary

What is known and objective: Adverse drug reactions (ADRs) are an important cause of mortality during medical care. To our knowledge, there are no studies in Ethiopia regarding the mortality rate from ADRs, characteristics of the reactions and the drugs implicated among patients presenting to hospital with community-acquired ADRs. Therefore, the aim of this study was to determine the mortality rate attributable to ADRs in patients presenting to hospital and identify drugs implicated in the ADR-related deaths at the Jimma University Specialised Hospital (JUSH), Southwest Ethiopia.

Methods: This cross-sectional study included 1,001 patients aged ≥18 years consecutively admitted to medical wards from May 2015 to August 2016. ADR-related mortality was determined through detailed review of medical records, laboratory tests, and patient interviews followed by causality assessment by the Naranjo algorithm and expert consensus.

Results: Of 1,001 patients, 15, 1.5% (95% confidence interval [CI]: 0.80-2.30%) died with an ADR. The primary suspected causes of death were drug-induced hepatotoxicity (7, 43.8%) followed by acute kidney injury (4, 25.0%). Isoniazid (6, 33.3%), pyrazinamide (3, 16.7%), efavirenz (2, 11.1%) and tenofovir (2, 11.1%) were commonly implicated drugs. The majority of ADRs (14, 93.8%) were preventable. Unadjusted bivariate comparisons suggested patients who died with ADRs were more likely to have pre-existing liver disease (40.0% vs. 7.0%; 95% confidence interval [CI]: 8.1-57.8%), a history of ADRs (40% vs. 1.4%; 95% CI: 13.8-63.4%), a lower mean (±SD) body mass index (BMI, 17.6 ± 2.1 vs. 20.0

± 2.9 kg/m^2; 95% CI=0.9-3.9), exposure to anti-tubercular (46.7% vs. 18.9%; 95% CI: 2.3-53.1%) and antiretroviral (40.0 % vs. 7.7%; 95% CI: 7.5-57.2%) therapies, and a higher mean number of medications (7.1 ± 3.3 vs. 3.8 ± 2.1; 95% CI: 2.2-4.4) and Charlson Comorbidity Index (3.9 ± 2.9 vs. 1.6 ± 1.8; 95% CI: 1.4-3.2) than surviving patients without ADRs.

What is new and conclusion: Fatal ADRs were common in patients presenting to hospital. The drugs implicated were mostly anti-tubercular and antiretroviral therapies, reflecting the high burden of HIV and tuberculosis in the study population. ADR-related deaths were significantly associated with poor nutritional status. The majority of ADR-related deaths were preventable, highlighting the need to develop a multidisciplinary approach to closely monitor patients who are prescribed anti-tubercular and antiretroviral therapies, particularly in patients with hepatic disease, a history of ADRs, who are malnourished, and who are exposed to multiple medications.

Key words: Adverse drug reaction; hepatic disease; malnutrition; mortality; Southwest Ethiopia

4.2 What is known and objective

Adverse drug reactions (ADRs) are an important cause of mortality during medical care (36). Globally, the rate of fatal ADRs in patients presenting to hospital has been reported to range from 0.1% to 10% (20, 37). Studies in developed countries reported that the rate of fatal ADRs ranged from 0.05% to 3% of all patients admitted due to an ADR (40, 61-63, 327). A recent review of 43 observational studies (where few studies were from developing countries) found that the median proportion of ADRs resulting in mortality in developing countries was 1.8% (interquartile range (IQR) 0.8-8.0%) which was similar to 1.7% (IQR 0.7-4.8%) in developed countries (22). However, there are major differences between developed and

developing countries in population demographics, disease distribution, drug therapy used and healthcare systems.

Treatment of epidemics and other infectious diseases are of particular concern in developing countries, where anti-tuberculosis (anti-TB) (34), antiretroviral (23), and antibacterial drugs (42, 64) are commonly associated with ADR-related hospitalisation. There is a 'double burden' in developing countries where there are rising rates of concomitant infectious and non-communicable diseases that require therapy with multiple medications with increased potential for interactions (273, 321). Unlike developed countries, there is: a high rate of mortality among HIV/tuberculosis infected patients on drug therapy (276), a less health-literate population (277), a lesser ability to provide healthcare (278), and a higher prevalence of malnutrition (279, 280).

There is substantial all-cause mortality rate among patients presenting to emergency departments in Ethiopia (275). There is increasing access to complex treatment of concomitant infectious and non-communicable diseases (268, 328), and a higher prevalence of concomitant anti-TB and antiretroviral therapy (ART) with overlapping adverse effects (270). Recent studies report a higher prevalence of drug-related problems (305) and irrational use of medicines among patients on chronic follow up in ambulatory care clinics (306).

Despite reporting of the burden of diseases, all-cause mortality, medication use patterns and associated adverse events, to our knowledge, there are no studies in Ethiopia regarding ADR-related mortality, characteristics of the reactions, and the drugs implicated among patients presenting to hospital with community-acquired ADRs. Therefore, the aim of this study was to determine the mortality rate attributable to ADRs in patients presenting to hospital, identify drugs implicated in the ADR-related deaths and identify factors contributing to ADR-related mortality at Jimma University Specialised Hospital (JUSH), Southwest Ethiopia.

4.3 Methods

4.3.1 Study design, setting and procedure

A cross-sectional study was conducted in patients consecutively admitted to general medical wards of JUSH from May 2015 to August 2016. JUSH is the major public teaching and referral hospital with a capacity of 600 beds in Southwest Ethiopia. The hospital provides general medical and specialised services for approximately 200,000 patients each year. The catchment population is 15 million (258).

Patients hospitalised due to ADRs and other causes were identified through detailed review of medical records, laboratory tests and patient interviews followed by Naranjo causality assessment and expert consensus meeting. ADRs were defined according to the definition of the World Health Organisation (WHO) (21), where treatment failure, drug abuse, intentional drug overdose, and accidental or self-poisoning were excluded. The first author (MTA), who was fully dedicated to this project, interviewed patients as soon as practical for socio-demographic information, social drug use, medical history, drug allergies, and use of over-the-counter and herbal medicines. MTA also reviewed each patient's medical records and medication exposure in the month preceding hospitalisation. Common laboratory tests were evaluated within 48 hours of admission for each patient case including renal function, serum electrolytes, liver function, and complete blood count. An ADR was suspected if there was a relationship between the time of drug administration and the onset and course of the adverse reaction, while excluding other potential causes. The *Naranjo ADR causality assessment scale* (88) was administered by the author (MTA) followed by ADR severity scaling using *the modified Hartwig et al.* method (46). A consensus review was performed between the first author and an internal medicine specialist to confirm the causal relationship of an ADR to the suspected medication using a similar approach to a previous study (65). Applying the Naranjo algorithm scores for definite and probable categories, we categorised patient admissions as

ADR-related or non-ADR-related. Subsequently, all deaths in the ADR-related group were considered to be definitely or probably associated with the ADR. ADRs observed during the hospital stay were excluded.

4.3.2 Definitions Used

ADRs that were suspected of causing death were classified as *preventable and non-preventable* using the principles of Schumock et al.. ADRs were classified as preventable if they met at least one of the following criteria: there was a previous reaction to the drug; if the drug, dose, route or frequency of administration involved was inappropriate for the patient; if there was a known treatment for the ADR; if the required therapeutic/laboratory monitoring test was not performed; if a drug interaction was involved; if poor medication compliance was involved; or if preventative measures were not prescribed.

For each patient, we determined the Charlson Comorbidity Index (CCI) (329), drug count, drugs implicated, HIV status, tuberculosis status, and other characteristics that could have been related to the patient's death. All-cause mortality refers to death from any cause (drugs and other medical illnesses). Adult nutritional status was assessed using the body mass index (BMI) (314) as underweight (<18.5 kg/m^2), normal (18.5-25 kg/m^2) and overweight (>25 kg/m^2). Drugs were classified using the WHO Anatomical Therapeutic Chemical Classification (ATC) System (310). Calculation of the number of medications was based on the number of active ingredients in single and combination products (312). Drug interactions were checked using the Micromedex-2 software followed by clinical judgment, and the severity levels were classified as contraindicated (avoid combination), major (consider therapy modification), moderate (monitor therapy) and minor interactions (no action needed) (330). All comorbidities were defined as present if documented in the medical records.

Patients were considered to have pre-existing chronic kidney disease if the eGFR was <60 mL/minute/1.73m^2, or they had documented abnormal renal ultrasounds (abnormal renal echogenicity or kidney size or presence of cysts) for at least 3 months prior to admission (315). Drug induced acute kidney injury was suspected among patients with baseline renal insufficiency (e.g., eGFR < 60 mL/minute/1.73m^2), volume depletion, and multiple exposures to nephrotoxic agents at admission, provided other potential causes of the admission were excluded. Chronic liver disease was considered pre-existing if liver diseases (such as cirrhosis, chronic viral hepatitis) or liver dysfunction or liver injuries were documented by the treating physician at/prior to admission (308). Drug-induced hepatotoxicity was considered when aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels were ≥3 times upper normal limit (UNL) or total bilirubin was ≥2 times UNL (316). The response to rechallenge or re-exposure to some drugs, such as anti-TB drugs, was applied by the treating physician using the WHO guideline for the treatment of tuberculosis (317).

4.3.3 Data entry, analysis and interpretation

Data were entered into a Microsoft Access 2016 database (Redmond, Washington) and analysed using SPSS version 23.0 Inc. (Chicago, Illinois). Independent variables were compared between patients who died with ADRs and patients who survived without ADRs using unadjusted bivariate analysis, unadjusted for effect modification or confounding. The chi-square test or Fisher's exact test were used to compare categorical data between patients who died with ADR and patients who survived without ADRs. Comparisons were performed for continuous variables using Student's t-tests with results presented as means and standard deviations (SD). Comparisons between patients who died with ADR (15 patients) and patients who survived without ADRs (797 patients) were presented using differences in proportions and means and 95% confidence intervals. Patients who died with other illnesses (101) and patients discharged alive after ADRs (88) were excluded from analysis to reduce

the heterogeneity, and subsequent confounding, in the comparator group. A p value of <0.05 was considered statistically significant in all analyses.

4.3.4 Ethics

The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (reference number H0014718) and Jimma University Institutional Review Board (reference number RPGC/58/2015). Written informed consent was obtained from all individual participants included in the study before collection of any information.

4.4 Results and discussion

Of the 1,001 patients, 103 patients were hospitalised due to ADRs. ADRs contributed to the death of 15 patients, which represented a mortality rate of 1.5% (95% confidence interval [CI]: 0.80-2.30%) in patients included in the study and 12.9% of all deaths (Fig 4.1). Studies conducted in South Africa (23), Iran (331), and India (64) reported comparable rates of ADR-related mortalities. However, the rate of ADR-related mortality in the current study was higher than the rates reported from Sweden (40), Finland (63) and the United Kingdom (47). This higher rate may be due to the growing use of polypharmacy in concomitant infectious and non-communicable diseases, a larger proportion of underweight patients with deranged pharmacokinetics and overlapping adverse effects of anti-TB and ART (162, 271). Alternatively, the variations in rates of fatal ADRs between studies and countries might be explained by differences in study design (prospective vs. retrospective), disease distribution, drug therapy used and healthcare systems.

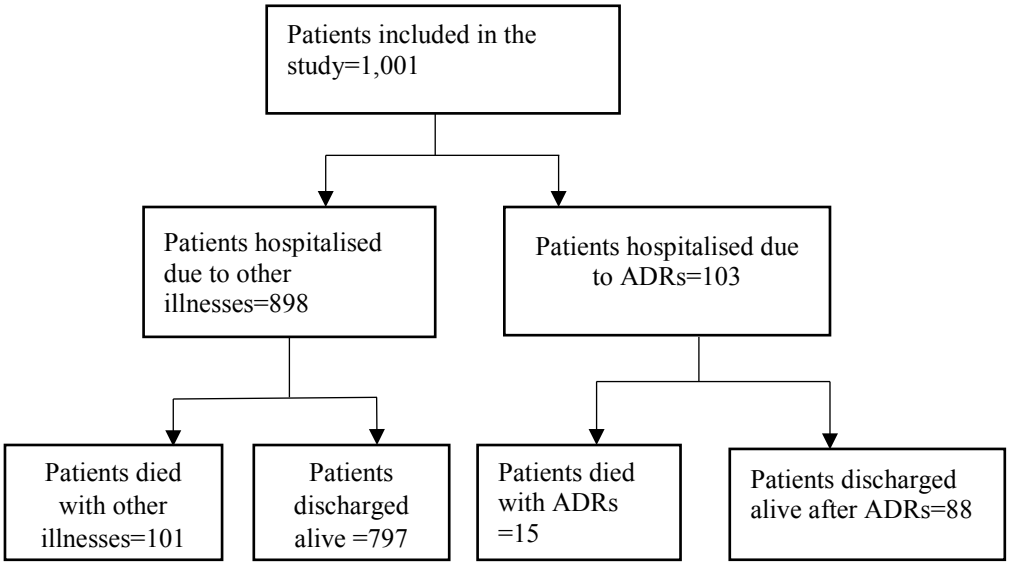


Figure 4. 1 Screening process for ADRs and ADR-related mortality

Malnutrition is one of the major public health problems in most developing countries, including Ethiopia (196). Unadjusted bivariate analysis suggested that patients died with ADRs had lower mean (± SD) BMI than patients alive without ADRs with a mean difference of 2.4 kg/m^2 (17.6 ± 2.1 vs. 20.0 ± 2.9; 95% CI: 0.9-3.9) (Table 4.1). Probable reasons include the pathophysiological changes encountered in nutrient deficiencies that interfere with pharmacokinetic and pharmacodynamic processes in the body, resulting in altered drug response (196). Malnutrition can also alter plasma and tissue protein quantitatively (197). Therefore, the plasma protein binding capacity for commonly used drugs, such as anti-inflammatory (diclofenac) and anti-TB drugs (pyrazinamide and isoniazid), might have been decreased resulting in an increased free fraction of the drug and hence ADRs. Forty percent of the patients who died with ADRs had liver diseases in the current study (Table 4.1). Patients with liver diseases are exceptionally vulnerable to developing malnutrition because of the key role played by the liver in regulating the nutritional state and the energy balance (198), which increases the risk of developing adverse clinical outcomes. There could have

been unintentional over dosage in patients with lower body weight or BMI that resulted in severe toxicity and subsequently death. Early and evidence-based nutritional interventions, especially in HIV/AIDS and tuberculosis patients, are strongly needed to minimise ADRs and ultimately improve the prognosis of such patients.

Table 4. 1 Unadjusted bivariate comparisons of clinical and demographic characteristics of patients discharged alive without ADRs and patients who died with ADRs

Variables	Total patients	Patients alive without ADRs	Patients died with ADRs	Difference between the proportions or means *	95% confidence interval *
Total patients	1,001	797	15		
Age, mean ± SD	42.4 ± 17.0	42.1 ± 16.9	44.5 ± 17.9	2.4	-6.3-11.1
Female, n (%)	455 (45.5)	360 (45.2)	7 (46.7)	1.5	-23.9-26.9
Previous ADR history, n (%)	41 (4.1)	11 (1.4)	6 (40.0)	38.6	13.8-63.4
Weight, mean ± SD	54.7 ±9.0	54.7 ± 8.9	53.2 ± 11.0	1.5	-3.1-6.1
BMI, mean ± SD	19.9 ± 2.9	20.0 ± 2.9	17.6 ± 2.1	2.4	0.9-3.9
Number of medications, mean ± SD	4.0 ± 2.3	3.8 ± 2.1	7.1 ± 3.3	3.3	2.2-4.4
Charlson Comorbidity Index, mean ± SD	1.9 ± 2.0	1.6 ± 1.8	3.9 ± 2.9	2.3	1.4-3.2
HIV/AIDS patients taking ART, n (%)	108 (10.8)	61 (7.7)	6 (40.0)	32.3	7.5-57.2
TB patients taking anti-TB drugs, n (%)	207 (20.7)	151 (18.9)	7 (46.7)	27.7	2.3-53.1
Pre-existing renal diseases, n (%)	61 (6.1)	38 (4.8)	2 (13.3)	8.6	-8.7-25.8
Pre-existing liver diseases, n (%)	90 (9.0)	56 (7.0)	6 (40.0)	33.0	8.1-57.8
Admissions (≥1) in the preceding 3 months#, n (%)	135 (13.5)	100 (12.5)	2 (13.3)	0.9	-16.6-18.1

#patients hospitalised before recruitment in the current study, * relates to the differences between patients alive without ADRs and patients who died with ADRs

The main suspected causes of death in the current study were hepatotoxicity (7, 43.8%) followed by acute kidney injury (4, 25.0%) and electrolyte disorders (2 [hypokalaemia, hypocalcaemia], 12.5%). Drugs frequently implicated in hepatotoxicity-related death included isoniazid (6, 33.3%) followed by pyrazinamide (3, 16.7 %) and efavirenz (2, 11.1%). Out of seven hepatotoxicity-related deaths, prophylactic isoniazid therapy was implicated in two of them (Table 4.2). Anti-TB drugs (isoniazid and pyrazinamide) and antiretroviral therapies (tenofovir and efavirenz) were frequently implicated in the ADR-related deaths, reflecting the high burden of HIV and tuberculosis and their associated drug-related problems in the study region. Isoniazid, the major hepatotoxic agent in the current study, was associated with the deaths of six patients in combination with pyrazinamide, rifampicin, efavirenz, nevirapine and ritonavir. Tenofovir, which is now being used in the majority of first-line highly active antiretroviral therapy regimens, was the single drug implicated in two ADR-related deaths due to acute kidney injury. Studies have shown that the decline in eGFR attributable to tenofovir was approximately 3-10 fold greater than the normal age-related decline (332, 333). Tenofovir-associated kidney injury and mortality is common, especially in patients with pre-existing renal disease, TB/HIV co-infection and concomitant anti-TB/HIV therapy (333, 334). This is in line with the results of this study. Tenofovir use in acutely ill patients with pre-existing renal diseases is of concern, particularly when tenofovir is co-prescribed with other potentially nephrotoxic drugs, as there are limited facilities for renal replacement therapy. Anti-infectives were also identified as the major causes of death in similar studies (335). In contrast, studies conducted in some high-income countries (10, 40, 63) reported that the most frequent fatal ADRs were gastrointestinal and intracranial haemorrhages attributed to antithrombotic agents, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. This is probably due to substantial differences in the burden of diseases and the drug therapies used between developed and developing countries. Similar

to developed countries, we identified ADR-related deaths associated with enalapril, diclofenac and metformin, at lower rates. This highlights the increasing double burden of ADRs associated with multiple drugs used in infectious and non-infectious diseases in Ethiopia.

A higher proportion of patients who died with ADRs had pre-existing liver diseases than those who did not as suggested in unadjusted bivariate analysis with a difference between the proportions of 33% (40% vs. 7%, 95% CI: 8.1-57.8%) (Table 4.1). Five of the seven patients who died from hepatotoxicity had overwhelmingly elevated AST and ALT levels that ranged from 6 to 50 times the UNL; medians (IQR) were 317.6 (228.8-991.2) U/L and 583.2 (227.3-789.2) U/L, respectively (Table 4.1). Slow acetylators of isoniazid are more susceptible to hepatotoxicity than rapid acetylators. (336, 337) The slow acetylation status has been shown to be the predominant phenotype in Ethiopian TB/HIV co-infected patients (271). Patients with prior liver diseases (338, 339) and lower BMI (malnutrition) (162) are also at higher risk of hepatotoxicity. Therefore, the combined effects of malnutrition, pre-existing liver diseases and slow isoniazid acetylation status in some Ethiopian patients may have contributed to the severe drug-induced hepatotoxicity that was a major cause of mortality in our study.

Nine of the 15 deaths occurred in patients with various combinations of HIV/AIDS, TB, low BMI (<18.5 kg/m^2) and pre-existing liver diseases (Table 4.2). Twenty-seven percent of ADR-related deaths were in patients with TB plus HIV/AIDS; this combination of comorbidities was seen in 4.1% of surviving patients. Similarly, TB plus pre-existing liver disease was seen in 27% of ADR-related deaths but only 1.4% of surviving patients. Low BMI with HIV/AIDS was seen in 27% of the ADR-related deaths and 2.8% of surviving patients; and low BMI with TB was present in 40% of ADR-related deaths compared to 8.2% of surviving patients (Table 2). Moreover, patients who died with ADRs had a higher CCI

than surviving patients without ADRs (3.9 ± 2.9 vs. 1.6 ± 1.8, 95% CI: 1.4-3.2) (Table 4.1). These findings highlight the high rates of interrelated comorbidities among the patients who suffered ADR-related deaths, potentially leading to increased medication regimen complexity. This, along with being immunocompromised, could have increased the risk of drug-drug and drug-disease interactions, deranged pharmacokinetics, serious ADRs and finally death.

According to the Schumock and Thornton preventability assessment criteria, two reactions (12.5%) were definitely preventable, 13 (81.3%) were probably preventable and one (6.2%) was not preventable (Table 4.2). Major underlying factors were poor therapeutic monitoring and the presence of clinically significant drug interactions that required therapy modification. The proportion of preventable ADRs in this study is comparable to previously described figures of 85.7% to 92% (35, 39). However, studies conducted in South Africa reported that only 45% (65) and 53% (23) of ADRs were preventable. The reason for this could be the difference in study design (prospective vs. retrospective identification of ADRs) and the nature of drugs used by the patients. In addition, there were more idiosyncratic reactions in the South African studies, possibly due to the larger number of patients with HIV-related immunodeficiency, where these type of reactions were mediated through a combination of immunologic (by dysregulation of the immune system on T and B-lymphocytes) and genetic factors (340).

Table 4. 2 Case details of ADR-related deaths

Drugs used by the patients prior to admission	Drug interaction severity level in drugs used by the patients prior to admission	Laboratory test results supportive of ADRs at admission	Significant comorbidities	ADR(s)[a] suspected of causing death	Drug(s) suspected in ADR-related death	Preventability of the ADR(s) using Schumock and Thornton criteria
Isoniazid, tenofovir, lamivudine, efavirenz, sulfamethoxazole, trimethoprim	Major	AST=317.6 U/L, ALT=583.2 U/L, ALP=1416.0 U/L, total bilirubin=3.5mg/dL	HIV/AIDS/ low BMI	Hepatotoxicity	Isoniazid, efavirenz	Probably preventable
Metronidazole, paracetamol, bisacodyl, tenofovir, lamivudine, efavirenz	None	Serum creatinine (SCr)=8.3 mg/dL, Blood Urea Nitrogen (BUN)=474mg/dL	HIV/AIDS/ liver diseases	Kidney injury	Tenofovir	Not preventable
Isoniazid, rifampicin, pyrazinamide, ethambutol	Major	AST=421.2 U/L, ALT=620.7 U/L, ALP=2223.8 U/L, total bilirubin=8.3	TB/low BMI/liver diseases	Hepatotoxicity	Isoniazid, pyrazinamide	Probably preventable
Glibenclamide, metformin, enalapril	Moderate	Scr=2.7 mg/dL, BUN=167.8 mg/dL	Type-2 diabetes, hypertension, stroke	Kidney injury and lactic acidosis	Enalapril, metformin	Probably preventable
Dexamethasone, trimethoprim, sulfamethoxazole, isoniazid, rifampicin, pyrazinamide, ethambutol, tenofovir, lamivudine, efavirenz	Major	AST=1750 U/L, ALT=789.2 U/L, ALP=570.0 U/L, total bilirubin=14.5	TB/HIV/AIDS/liver diseases	Hepatotoxicity	Isoniazid, pyrazinamide	Probably preventable
Tenofovir, lamivudine, nevirapine, omeprazole, metoclopramide, isoniazid, sulfamethoxazole, trimethoprim	Major	AST=284.5 U/L, ALT=227.3 U/L, ALP=388.0 U/L, total bilirubin=5.1	HIV/AIDS	Hepatotoxicity	Isoniazid, nevirapine	Probably preventable
Tenofovir, lamivudine, efavirenz sulfamethoxazole, trimethoprim, rifampicin, ethambutol	Major	AST=991.2 U/L, ALT=11450.0 U/L, ALP=2045.0 U/L, total bilirubin=3.2 mg/dL	TB/HIV/AIDS/low BMI/liver diseases	Hepatotoxicity	Efavirenz	Definitely preventable
Isoniazid, rifampicin, pyrazinamide, ethambutol, tenofovir, lamivudine, efavirenz, pyridoxine, sulfamethoxazole, trimethoprim	Major	Scr=3.2 mg/dL, BUN=72.4 mg/dL	TB/HIV/AIDS/low BMI	Kidney injury	Tenofovir	Probably preventable
Isoniazid, rifampicin, pyrazinamide, ethambutol, pyridoxine, heparin, azithromycin, cimetidine, metoclopramide, diclofenac, paracetamol, dexamethasone	Major	AST=228.8 U/L, ALT=223.4 U/L, ALP=321.0 U/L, total bilirubin=3.0 mg/dL	TB/low BMI/liver diseases	Hepatotoxicity	Isoniazid, pyrazinamide	Definitely preventable
Diazepam, heparin, phenytoin, digoxin, cimetidine, thioridazine	Major	-	Epilepsy, stroke, rheumatic heart diseases	Falls	Diazepam, thioridazine	Probably preventable
Furosemide, prednisolone, isoniazid, rifampicin, pyrazinamide, ethambutol	Major	Serum calcium=4.5 mEq/L	TB/low BMI	Hypocalcaemia	Furosemide, prednisolone[b]	Probably preventable
Furosemide, acetylsalicylic acid, metoprolol, atorvastatin, enalapril, hydrochlorothiazide, diclofenac	Major	Scr=4.7mg/dL, BUN=125mg/dL	Ischaemic heart disease, congestive heart failure	Kidney injury	Enalapril, diclofenac	Probably preventable
Tenofovir, lamivudine, ritonavir, lopinavir, isoniazid, rifampicin, cimetidine, ferrous sulphate	Major	AST=210 U/L, ALT=246.4 U/L, ALP=415.0 U/L, total bilirubin=3.7 mg/dL	TB/HIV/AIDS/low BMI	Hepatotoxicity	Isoniazid, rifampicin, ritonavir	Probably preventable
Acetylsalicylic acid, digoxin, furosemide	Moderate	Serum potassium=2.1 mEq/L	Rheumatic heart disease, congestive heart failure	Hypokalaemia	Furosemide, digoxin	Probably preventable
Furosemide, tramadol, enalapril, acetylsalicylic acid, clopidogrel, heparin	Major	-	Acute myocardial infarction and ascites	GI bleeding	ASA[c], clopidogrel, heparin	Probably preventable

[a]all ADRs were classified as level 7 according to modified Hartwig et al. method, [b] possible causality in Naranjo scale, [c] acetylsalicylic acid (ASA) dose ≥300mg

Limitations of this study were that some questions in the Naranjo causality assessment tool were not feasible nor ethical for clinical practice, such as observing effects on giving placebo. Inter-rater reliability agreement was not measured for ADR causality, although consensus was reached in all cases. The study only identified death due to ADR-related admissions to hospital, not in-hospital ADRs, nor patients who died before presenting to hospital, so our results may have underestimated the full burden of ADR-related mortality. Severely obtunded and critically ill patients who were not able to be interviewed were excluded from the study. This might have underestimated the proportion of death in both the ADR and non-ADR groups. Commonly used over-the-counter medicines, contraceptives, topical agents, and herbal remedies were not commonly recorded in drug histories, which may have influenced the findings of this study. Multivariable regression analysis was not conducted due to overfitting because of the low number of deaths, therefore, the results may be impacted by confounding. The results of this study should be extrapolated to other countries with caution, as the study findings depend on the patient characteristics, disease distribution, healthcare infrastructure, ADR detection methods and definitions of ADRs adopted.

However, despite its limitations, this study is relevant to healthcare authorities, programme leaders and policy makers, as it describes one of the major drug-related problems that is little known in the region. We used a three-step process in ADR assessment, evaluating individual patients' clinical and laboratory parameters; causality and preventability assessment; followed by consensus review, to help mitigate the subjectivity associated with interpretation of some ADRs. A yearlong sampling period avoided the bias associated with anti-infective use patterns due to seasonal variation.

4.5 What is new and conclusion

Fatal ADRs were common in patients presenting to medical wards of the JUSH. Unlike in high-income countries, isoniazid and pyrazinamide-induced hepatotoxicity followed by

tenofovir-induced kidney injury were the major suspected causes of mortality, reflecting the high burden of HIV and tuberculosis in the study setting. ADR-related deaths were significantly associated with poor nutritional status. The majority of ADR-related deaths were preventable, highlighting the need to develop a multidisciplinary approach to closely monitor patients who are prescribed anti-tubercular and antiretroviral therapies, particularly in patients with hepatic disease, a history of ADRs, who are malnourished, and who are exposed to multiple medications. Drug-drug interactions were the major challenges in ADR causality assessment especially in patients taking fixed dose combination of anti-TB drugs and ART. On-the-job training and follow-up of medical practitioners, especially physicians and clinically trained pharmacists, focusing on preventable ADRs and effective use of a pharmacovigilance system should be considered at emergency and ambulatory care units of all healthcare levels to monitor drug response in patients to minimise the ADR-related burden.

Chapter Five

5. Drug-induced hepatotoxicity-related hospitalisation: Patterns, severity and implicated drugs

5.1 Abstract

Background: Drug-induced-hepatotoxicity (DIH) is responsible for over 50% of cases of acute liver failure and 0.1-5% of all hospital admissions. However, little is known about DIH-related hospitalisation in Ethiopia.

Objective: The aim was to determine the prevalence, severity and clinical patterns of DIH-related hospitalisation and identify commonly implicated drugs.

Methods: Ethiopian patients aged ⩾18 years, taking at least one regular medication prior to hospital admission and who had at least one set of liver function tests were included. DIH-related hospitalisation was identified through evaluation of patient history, clinical and biochemical characteristics and causality assessment of likely precipitating drug(s) followed by expert consensus. DIH severity was classified using the Drug-Induced Liver Injury Expert Working Group criteria. The R-value was used to define patterns of liver injury.

Results: Of 674 patients, 35 (5.2%) were hospitalised due to DIH. Twenty-two patients (62.9%) exhibited a cholestatic pattern, followed by eight (22.9%) with a hepatocellular pattern. Commonly implicated drugs were isoniazid (21, 60.0%), pyrazinamide (16, 45.7%), efavirenz (5, 14.3%), nevirapine (5, 14.3%) and atorvastatin (5, 14.3%). More than two-thirds of cases (24, 68.6%) were severe or fatal; these were mainly caused by anti-tuberculosis (anti-TB) drugs (15, 42.9%), antiretroviral therapy (ART) (4, 11.4%) or concomitant anti-TB/ART (6, 17.1%).

Conclusion: DIH is an important cause of hospitalisation and mortality in Ethiopia. Most cases were cholestatic and caused by anti-TB agents and ART. Special consideration should be given to patients taking anti-TB drugs and ART, particularly those with malnutrition, pre-existing liver disease and previous ADR history.

5.2 Introduction

Drug-induced hepatotoxicity (DIH) is a frequent cause of liver injury (341). The true incidence of DIH for community-based patients is largely unknown due to a scarcity of population-based studies, under-reporting of adverse reactions and multiple confounding factors in the diagnosis (342). However, the incidence of DIH is likely to rise in the general population because of the increasing number of drugs used in medical care (342, 343). According to a 2017 Council for International Organizations of Medical Sciences working group report on drug-induced liver injury (DILI), the hepatotoxic potential of a drug can only be recognised through post-marketing surveillance (344). For most medications, the risk of DIH is higher than reported in initial clinical trials (342, 345-347). Antimicrobials have been reported to be the major cause of DIH worldwide (138, 348), with amoxicillin and flucloxacillin commonly implicated in developed countries (349) and anti-tuberculosis (anti-TB) drugs in developing countries (350). DIH is responsible for over 50% of acute liver failure (133, 134) and between 0.1% and 5% of hospital admissions (351, 352). DIH has profound implications for morbidity, mortality and healthcare expenditure (136).

Studies have revealed that hospital admissions for DIH have increased steadily over the last three decades due to an aging population, access to multiple medications and dietary supplements with potential for hepatotoxicity, chronic illness, and infectious diseases (57, 132, 133, 353). Risk factors for DIH include genetics, younger and older age, female gender, pregnancy, malnutrition, obesity, diabetes mellitus, pre-existing liver disease, human

immunodeficiency virus (HIV), smoking, alcohol consumption, and infections or inflammatory episodes (354-356). Many of these factors are common in the Ethiopian population. The ongoing epidemics of HIV/AIDS and TB, plus the emergence of chronic non-infectious diseases due to increasing life expectancy, mean that the exposure to hepatotoxic drugs in this population is likely to increase. We previously identified DIH as the most common cause of adverse drug reaction (ADR)-related admission in a hospital in Southwest Ethiopia (147), highlighting its importance in this clinical setting. To our knowledge, there are no studies investigating the prevalence, severity and patterns of DIH-related hospitalisation for community-based patients in Ethiopia. Therefore, the aim of this study was to determine the prevalence, severity and clinical patterns of DIH and identify drugs commonly implicated in DIH-related admission to Jimma University Specialised Hospital (JUSH), Southwest Ethiopia.

5.3 Methods

This is a sub-study of a prospective observational study investigating ADR-related admissions at JUSH from May 2015 to August 2016 (147). JUSH is the major public teaching and referral hospital with a capacity of 600 beds in Southwest Ethiopia. The hospital provides general medical and specialised services for approximately 200,000 patients each year. The catchment population is 15 million.

Criteria for this sub-study were: age $\geqslant$18 years, taking at least one regular medication prior to hospital admission, documentation of at least one set of liver function tests including AST (aspartate aminotransferase), ALT (alanine aminotransferase), ALP (alkaline phosphatase) and total bilirubin at admission, and presence of complete records of past medical and medication history at admission. Suspected DIH-related hospitalisation was based on the relationship between the time of drug administration and the onset and course of the adverse reaction, the patient's history and clinical and biochemical characteristics, combined with a drug known to

cause liver injury, and exclusion of other forms of liver disease. Patients admitted with a confirmed diagnosis of acute viral hepatitis (patients with positive serological tests for hepatitis virus), and autoimmune or metabolic liver disease (haemochromatosis, biliary obstruction, alcohol-induced) were excluded from analysis. Patients were classified as having pre-existing liver disease if liver diseases (such as cirrhosis, chronic viral hepatitis) or liver dysfunction or liver injury were documented by the treating physician at, or prior to admission (308).

Patients with a principal admission diagnosis of DIH were identified. Additionally, patients with DIH were identified using biochemical diagnostic criteria from any of the following:

- ALT/AST ⩾5 times upper limit of normal (ULN);
- ALP ⩾2 times ULN;
- ⩾3-fold elevation in ALT with simultaneous elevation of bilirubin exceeding twice ULN, and
- Any increase in AST and/or ALT levels together with anorexia, nausea, vomiting, and jaundice provided other causes were excluded (141, 357).

Confirmation of the causal relationship between DIH-related hospitalisation and the suspected medication was performed using the Naranjo ADR assessment scale (88), followed by clinical consensus between the authors (clinical pharmacist MTA and internal medicine specialist DY). We considered DIH with definite, probable and possible causality.

According to the DILI Expert Working Group (358), the ULN of AST, and ALP was 41 U/L, and 128 U/L, respectively. The ULN of ALT for men and women were 33 U/L and 29 U/L, respectively. Hyperbilirubinemia was considered when the serum total bilirubin level was >1.0 mg/dL. Hypoalbuminemia was considered when the serum albumin level was <3.5 g/dL. Adult nutritional status was assessed using the body mass index (BMI) (314) and classified as <18.5

kg/m^2 and ≥ 18.5 kg/m^2 for analysis. The patterns of DIH were defined based on the R-value or ALT and ALP levels (348, 358). The R-value is calculated as ALT/ULN divided by ALP/ULN (Table 1). However, patterns of DIH may vary for the same drug.

Table 5. 1. Definition and classification of the patterns of DIH

DIH pattern	R-value	Predominant liver enzyme
Hepatocellular	⩾5	ALT ≥3 ULN
Cholestatic	≤2	ALP ≥2 ULN
Mixed	2<R<5	ALT >3 ULN and ALP >2 ULN

The severity of DIH was classified as defined by the DILI Expert Working Group (358) based on the liver function test values at admission as:

- Grade 1: 1.25–2.5 x ULN, or mildly elevated ALT or ALP reaching criteria for DIH but bilirubin <2 x ULN;
- Grade 2: 2.6–5.0 x ULN, or moderately elevated ALT or ALP reaching criteria for DIH and total bilirubin ≥2 x ULN;
- Grade 3: 5.1–10 x ULN, or severely elevated ALT or ALP reaching criteria for DIH and total bilirubin ≥2 x ULN and one of the following: INR ≥1.5, ascites, encephalopathy, disease duration <26 weeks, absence of underlying cirrhosis, and/or other organ failure considered due to DIH; and
- Grade 4: >10 x ULN, or death or required transplantation of liver.

Based on the clinical signs, symptoms and liver function tests at discharge, DIH was classified as recovered (the signs and symptoms were resolved and liver enzyme levels returned to normal range), did not recover (patients discharged or referred to other settings with the presence of signs and symptoms and/or abnormal liver enzyme levels) and fatal.

Data was recorded into an Access database (Microsoft 2016, Redmond, Washington) and analysed using the IBM Statistical Package for the Social Sciences (IBM SPSS version 23.0 Inc., Chicago, Illinois). Categorical variables were presented as frequencies and percentages whereas continuous variables were presented as mean ± standard deviations or median (interquartile range).

The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee and the Jimma University Institutional Review Board. Written informed consent was obtained from all patients included in the study.

5.4 Results

5.4.1 Socio-demographic and clinical characteristics of DIH patients

Of the 1,001 patients included in the original prospective observational study, 674 (369 males and 305 females) fulfilled the inclusion criteria for this sub-study. Of these, 35 (5.2%) were hospitalised due to DIH (Fig 5.1). Over half of the DIH patients were underweight (18, 51.4%) and had pre-existing liver disease (19, 54.3%). Their mean number of medications was 7.0 ± 2.8. Sixty percent of the patients with DIH had been using anti-TB drugs, and 12 (34.3%) were on ART. Eleven (31.4%) had a previous ADR history. Their mean length of stay (LOS) was 15.6 ± 9.9 days (Table 5.2).

The median AST and ALT serum levels were at least six times above the ULN and median bilirubin was three times above the ULN. Ten patients (28.6%) recovered, 18 (51.4%) did not recover prior to discharge and seven (20.0%) died. The majority (70.0%) of the patients who recovered from DIH exhibited a cholestatic pattern. Of seven DIH-related deaths (two males and five females), four were cholestatic, two were hepatocellular, and one was mixed. The

median time for the onset of DIH after the initiation of the suspected drug was 22 (IQR 15-34) days (Table 3).

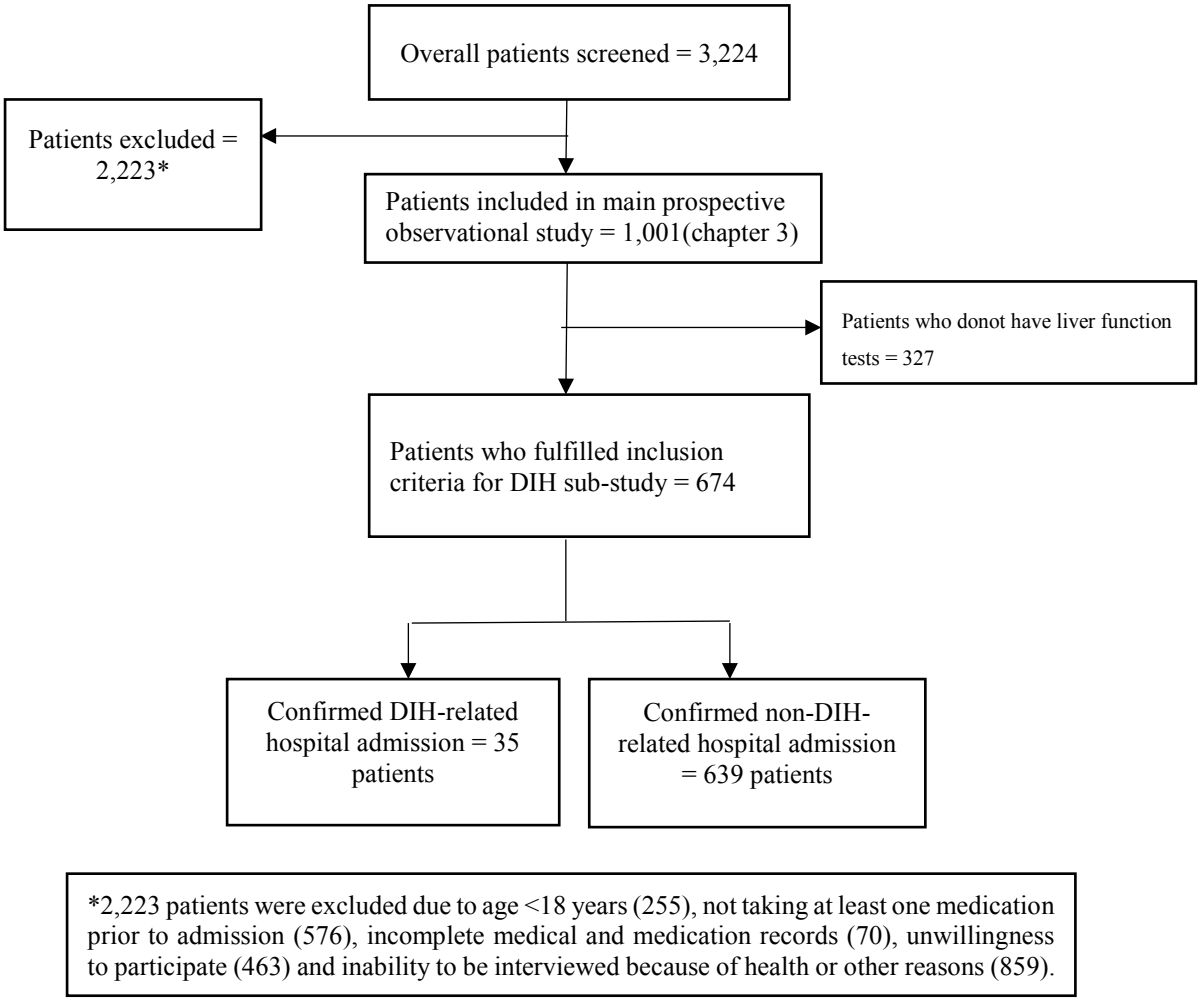


Figure 5. 1 Flow diagram of DIH-related hospital admission assessment procedure

5.4.2 Drugs implicated in DIH

Overall, 239 drugs were being taken by the 35 DIH patients; of these, 64 drugs were suspected to be implicated in DIH-related hospital admissions. The most frequent drug classes implicated were anti-TB drugs (21 patients, 60.0%) followed by ART (12 patients, 34.3%). Specific drugs most commonly implicated were isoniazid (21, 60.0%), pyrazinamide (16, 45.7%), efavirenz (5, 14.3%), nevirapine (5, 14.3%) and atorvastatin (5, 14.3%). Patients taking anti-TB drugs

were unintentionally overdosed according to their respective body weight in 11 cases (31.4%) (Table 5.3).

5.4.3 DIH biochemical patterns, severity and associated drugs

The majority of DIH biochemical patterns were cholestatic (22, 62.9%) followed by hepatocellular (8, 22.9%) and mixed (5, 14.3%). Over two-thirds (68.6%) of cases of DIH were severe (grade 3) and fatal/required liver transplantation (grade 4). All cases of hepatocellular and mixed DIH, and half of the cases of cholestatic DIH, were classified as grade 3 and 4. Fifteen (43%) of the DIH cases were suspected to be caused by anti-TB drugs alone, followed by anti-TB/ART combinations (6, 17.1%) and ART only (4, 11.4%). Most (83%) of the severe and fatal (grade 3 and grade 4) DIH was suspected to be caused by anti-TB drugs alone (11/24, 45.8%), followed by anti-TB/ART combinations (5/24, 20.8%) and ART alone (4/24, 16.7%) (Table 5.4).

Table 5. 2. Socio-demographic and clinical characteristics of patients with and without DIH at admission

Variables at admission	Patients without DIH, N=639	Patients with DIH, N=35
Age, mean ± SD	42.0 ± 16.9	43.7 ± 19.4
Male, n (%)	352 (55.1)	17 (48.6)
BMI*<18.5 kg/m^2, n (%)	196 (30.7)	18 (51.4)
Number of medications*, mean ± SD	4.0 ± 2.2	7.0 ± 2.8
Alcohol consumers, n (%)	143 (22.4)	5 (14.3)
Herbal remedies users, n (%)	53 (8.3)	3 (8.6)
Smokers, n (%)	45 (7.0)	3 (8.6)
Anti-TB drugs*, n (%)	141 (22.1)	21 (60.0)
ART*, n (%)	66 (10.3)	12 (34.3)
Patients with pre-existing liver diseases*, n (%)	60 (9.4)	19 (54.3)
Patients with previous ADR history*, n (%)	21 (3.3)	11 (31.4)
Had at least one chronic illness*, n (%)	234 (36.6)	27 (77.1)
Length of stay, mean ± SD	13.4 ± 8.0	15.6 ± 9.9

* $p<0.005$

Table 5 3. Case details of patients with DIH

Sex/Age	BMI	Suspected drug(s)	Clinical presentation, other laboratory results and associated diagnosis	AST* (ULN= 41 U/L)	ALT* (ULN= 33 U/L for male & 29 for female)	ALP* (ULN= 128 U/L)	Total Bilirubin (normal range: 0.1-1 mg/dL)*	Serum Albumin (normal range: 3.5-5 g/dL)*	Pattern of DIH using R-value	Anti-TB/ ART combi-nation	Patient outcome
F/24	18.3	Isoniazid, pyrazinamide, rifampicin	Easy fatigability, vomiting, high-grade fever and epigastric pain	229.0	219.0	461.0	NA	2.4	Cholestatic	No	Not recovered
F/35	19.8	Isoniazid, pyrazinamide	Vomiting, yellow discoloration of eyes, anorexia and ascites	277.8	301.0	1262.8	4.1	2.9	Cholestatic	No	Not recovered
F/58	16.9	Propylthiouracil	Epigastric pain, nausea and vomiting	186.7	173.1	393.0	0.9	NA	Cholestatic	No	Recovered
F/47	15.5	Phenytoin	Abdominal pain, vomiting, wasting syndrome and negative hepatitis B surface antigen	317.6	583.2	1416.0	3.5	1.5	Cholestatic	No	Not recovered
M/30	16.5	Isoniazid, pyrazinamide	Tiredness, fatigue and negative hepatitis B surface antigen	337.4	179.3	1192.4	NA	2.4	Cholestatic	No	Not recovered
M/38	22.3	Isoniazid, rifampicin, ritonavir	Yellow discoloration of eyes and skin, itchy skin, ascites and negative hepatitis B surface antigen	210.0	246.4	415.0	3.7	NA	Mixed	Yes	Died
M/75	22.4	Atorvastatin	Abdominal pain and negative hepatitis B surface antigen	627.0	2226.6	1271.6	1.5	4.7	Hepatocellular	No	Not recovered
M/29	18.3	Efavirenz	Right upper quadrant abdominal pain, yellow discoloration of eyes, vomiting, and negative hepatitis B surface antigen	1500.0	789.2	570.0	14.5	NA	Hepatocellular	No	Not recovered
M/21	13.7	Isoniazid, pyrazinamide	Vomiting, mucoid diarrhoea, yellow discoloration of eyes, wasting syndrome and negative hepatitis B surface antigen and hepatitis C virus	263.2	2103.0	387.3	10.6	1.2	Hepatocellular	No	Recovered
M/60	17.2	Nevirapine	Abdominal pain, vomiting and negative hepatitis B surface antigen	246.2	320.9	790.0	NA	NA	Cholestatic	No	Recovered
F/55	22.6	Isoniazid, pyrazinamide, efavirenz	Vomiting, abdominal pain, swallowing difficulty and negative hepatitis B surface antigen	196.2	159.7	326.6	4.2	4.0	Cholestatic	Yes	Recovered
F/40	19.2	Isoniazid, pyrazinamide	Yellow discoloration of eyes, watery diarrhoea and vomiting.	421.2	620.7	2223.8	8.3	1.7	Cholestatic	No	Died
F/28	19.7	Isoniazid, pyrazinamide	Yellow discoloration of eyes, nausea, vomiting and diarrhoea	183.3	140.0	277.2	3.1	1.6	Cholestatic	No	Recovered
M/40	15.1	Isoniazid, rifampicin, atazanavir	Wasting syndrome, loss of appetite, fever, ascites and negative hepatitis B surface antigen	991.2	1269.9	845.0	3.2	2.4	Hepatocellular	Yes	Not recovered
M/33	15.9	Nevirapine	Generalised body rash, fatigue, wasting syndrome, yellow discoloration of eyes mucosa, difficulty of swallowing	169.0	141.9	311.3	3.0	1.7	Cholestatic	No	Not recovered
M/24	17.3	Isoniazid, pyrazinamide	Weight loss, fatigue, diarrhoea, high grade fever, and global headache	496.8	302.1	1234.7	1.1	NA	Cholestatic	No	Not recovered
F/40	13.3	Isoniazid, efavirenz	Wasting syndrome, abdominal pain and vomiting	317.6	583.2	1416.0	3.5	2.2	Cholestatic	Yes	Died
F/28	22.3	Isoniazid, pyrazinamide	Vomiting, loss of appetite, easy fatigability, severe anaemia and encephalopathy	786.9	1320.1	976.1	NA	3.5	Hepatocellular	No	Not recovered
F/55	19.8	Isoniazid, pyrazinamide, efavirenz	Yellow discoloration of eyes, abdominal pain and vomiting	126.9	298.0	627.0	NA	NA	Cholestatic	Yes	Recovered

Sex/Age	BMI	Suspected drug(s)	Clinical presentation, other laboratory results and associated diagnosis	AST* (ULN= 41 U/L)	ALT* (ULN= 33 U/L for male & 29 for female)	ALP* (ULN= 128 U/L)	Total Bilirubin (normal range: 0.1-1 mg/dL)*	Serum Albumin (normal range: 3.5-5 g/dL)*	Pattern of DIH using R-value	Anti-TB/ ART combi-nation	Patient outcome
F/65	14.2	Isoniazid	Yellow discoloration of skin, wasting, abdominal pain, vomiting	238.8	221.2	474.9	NA	1.6	Cholestatic	No	Died
F/28	15.6	Isoniazid, pyrazinamide	Wasting, difficulty of eyes opening, and abdominal discomfort and weakness	228.8	223.4	481.0	3.0	NA	Cholestatic	No	Recovered
M/33	20.2	Nevirapine, clopidogrel, atorvastatin	Abdominal pain, vomiting, negative hepatitis B surface antigen	115.7	325.8	727.6	NA	2.2	Cholestatic	No	Recovered
M/65	17.9	Phenytoin	Abdominal pain, nausea, vomiting and mental confusion	979.6	862.1	1689.0	NA	3.6	Cholestatic	No	Not recovered
M/33	16.9	Nevirapine, clopidogrel, atorvastatin	Poor appetite, yellow discoloration of eyes, high grade fever, encephalopathy and negative hepatitis B surface antigen	185.4	146.4	415.5	3.7	1.6	Cholestatic	No	Not recovered
M/65	20.1	Isoniazid, pyrazinamide	Malaise, abdominal pain and vomiting	1286.0	1270.0	513.0	NA	2.6	Hepatocellular	No	Not recovered
M/95	21.8	Omeprazole	Abdominal pain, yellow discoloration of eyes and urine, nausea, vomiting, and fatigue	745.1	1296.3	1456.0	NA	NA	Mixed	No	Not recovered
M/80	19.6	Atorvastatin	Yellow discoloration of skin and abdominal pain	136.6	160.3	360.0	3.2	NA	Cholestatic	No	Not recovered
F/24	20.8	Isoniazid, pyrazinamide	Loss of appetite, nausea, vomiting, ascites and fatigue	184.6	194.9	256.1	NA	1.9	Mixed	No	Not recovered
M/68	23.9	Efavirenz	Abdominal pain, yellow discoloration of eyes and dark urine, nausea, vomiting and weakness	177.0	122.2	667.0	4.7	NA	Cholestatic	No	Died
M/48	18.4	Isoniazid, pyrazinamide	Abdominal pain, yellow skin, nausea, vomiting, encephalopathy and tiredness	991.2	1145.0	2045.0	3.2	NA	Mixed	No	Recovered
F/26	18.0	Propylthiouracil	Weight loss, poor appetite, vomiting and malaise	200.0	132.0	321.0	NA	NA	Cholestatic	No	Not recovered
F/25	20.6	Isoniazid, pyrazinamide	Abdominal distension, yellow discoloration of eyes, and chronic viral hepatitis B	1750.0	789.2	570.0	14.5	1.6	Hepatocellular	No	Died
F/21	16.6	Isoniazid, nevirapine	Abdominal discomfort, yellow discoloration of eyes, vomiting and mental confusion	740.5	980.5	457.6	NA	NA	Hepatocellular	Yes	Died
F/28	19.8	Atorvastatin	Abdominal pain, yellow discoloration of eyes, vomiting and coma	284.5	227.3	570.0	5.1	2.6	Mixed	No	Recovered
F/65	22.3	Isoniazid, pyrazinamide	Abdominal pain, yellow discoloration of skin and urine, nausea, vomiting and fatigue	156.0	217.6	1678.0	NA	NA	Cholestatic	No	Not recovered

Note: * liver function tests at admission, NA=Not available, M=Male, F=Female

Table 5. 4. Severity of DIH with regard to the patterns and commonly implicated major drug classes

Patterns of DIH using R-value	**Severity level, n (%)**	
	Non-severe[a]	**Severe/fatal[b]**
Cholestatic	11 (50.0)	11 (50.0)
Hepatocellular	0 (0.0)	8 (100.0)
Mixed	0 (0.0)	5 (100.0)
Total Patients	11 (31.4)	24 (68.6)
Major drug groups implicated	**Non-severe[a]**	**Severe/fatal[b]**
Anti-TB drugs only, n (%)	4 (26.7)	11 (73.3)
ART only, n (%)	0 (0.0)	4 (100.0)
ART and anti-TB drugs only, n (%)	1 (16.7)	5 (83.3)

Annotations: [a] grade 1 and 2 that represents patients who present with elevated level of liver enzymes/bilirubin and/or serum albumin without signs/symptoms, [b] grade 3 and 4 that represent patients who present with both elevated liver enzymes/bilirubin and typical clinical signs and symptoms.

5.5 Discussion

The prevalence of DIH-related hospital admission in this study was 5.2%, which highlights the substantial impact of the problem in community-based Ethiopian patients. Studies conducted in the United States (351) and Sweden (359) reported comparable results for the prevalence of DIH-related hospitalisation, while studies from South Korea (360) and Thailand (361) have reported that 1.1% and 1.2% of hospital admissions were due to DIH, respectively. These differences might be due to variations in population characteristics, drug therapies and DIH detection methods employed. In addition, there might be differences in the nature of DIH due to wide spectrum patterns of manifestations, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure. Moreover, the DIH analysis in this study was performed in a selected group of admissions - only in 674 of more than 3,000 screened. While there are no directly comparable studies from Ethiopia, three studies have reported on the prevalence of DIH in patients with TB and HIV in follow-up clinics (162, 362, 363), where DIH-related hospitalisation was not described. These studies showed a higher prevalence of DIH (8.0-15.0%), most likely due to a higher use of hepatotoxic anti-TB/ART compared to the general population admitted to hospital in the current study.

The cholestatic pattern was more common than hepatocellular or mixed patterns, which is in line with another Ethiopian study (363). Also in agreement with other studies (363, 364), anti-TB drugs (e.g. isoniazid, pyrazinamide) followed by ART (e.g. efavirenz) and statins (e.g. atorvastatin) were frequently suspected to cause cholestatic DIH. In addition, the presence of a significant proportion of patients with malnutrition and pre-existing liver diseases could have heightened the risk of developing cholestatic DIH (136, 364). Moreover, in patients taking multiple drugs, some drugs causing enzyme inhibition might have increased the plasma concentration of concomitantly used drug(s) so that the risk of overlapping toxicities have been accentuated. Prompt recognition of DIH based on the available clinical and biochemical data

and appropriate management based on existing guidelines such as the WHO TB treatment guidelines (365) may avoid chronic consequences. In the current study, only ten patients (28.6%) recovered spontaneously whereas seven (20.0%) died and the outcome of more than half of the patients was unknown. Although progression to chronic DIH was not observed in our study, early assessment of the pattern of DIH is vital for preventing progression to chronicity and even death (136, 348).

The drug classes commonly implicated in DIH were anti-TB and ART, which is in line with other studies (138, 162, 343, 348). Most of the DIH-related hospitalisations were associated with anti-TB drugs, primarily isoniazid in the current study. There were a number of factors influencing the toxicity of isoniazid. As with other hepatotoxicity studies (162, 339, 366, 367), many DIH patients were underweight. The depletion of glutathione stores in malnourished patients increases vulnerability to oxidative liver injury (368). Some patients had increased susceptibility to isoniazid/pyrazinamide-associated hepatotoxicity because of concomitant retroviral infection leading to a mild inflammatory reaction and increased pharmacokinetic drug interactions (369). Polymorphisms of the key enzymes in the metabolic pathway of isoniazid, N-acetyltransferase 2 and microsomal enzyme cytochrome P4502E1, influence isoniazid-induced hepatotoxicity through increased formation of toxic metabolites (370). A study conducted by Yimer et al. (271) in Ethiopian patients on ART and anti-TB drugs revealed a greater proportion of the slow acetylator phenotype compared to other populations that may have increased the risk for isoniazid-related hepatotoxicity. Additionally, fixed dose anti-TB drugs (predominantly isoniazid) were unintentionally overdosed in eleven patients based on their body weight, which could have contributed to severe DIH.

We found the median time to the occurrence of DIH was within the first 3 weeks of suspected drug initiation, mainly of anti-TB drugs and ART, which is similar to the results of another

study (362). The WHO recommends initiation of ART within 8 weeks of initiation of anti-TB therapy or within 2 weeks in TB patients with a CD4 count of less than 50 cells/mm^3 (365). However, concomitant use of anti-TB agents and ART leads to concerns about drug interactions, clinical deterioration from immune reconstitution inflammatory syndrome, and overlapping toxicities. Conversely, delays in ART initiation in TB patients may result in AIDS-related illness and death (365). The decision regarding initiation of either therapy at the recommended time as per WHO (365) and Ethiopian treatment guidelines for concomitant TB/HIV infection requires a pre-treatment evaluation by a multidisciplinary team involving physicians, nurses, pharmacists, and other health professionals. Our findings and the limited related literature (354-356) suggest that this pre-treatment evaluation should include, but not be limited to, screening for pre-existing liver disease, history of excess alcohol consumption, previous ADR history, nutritional status, baseline serology for chronic viral infections (hepatitis B, C and HIV), and assessment of the benefit of empirical treatment initiation of anti-TB/ART versus the risk of adverse outcomes.

Given the majority of DIH-related hospitalisation and mortality occurred in patients receiving anti-TB agents (especially isoniazid and pyrazinamide) and ART, principally in underweight patients with pre-existing liver diseases, the following approaches could be considered to minimise the occurrence of preventable DIH:

- Patients should be educated about the importance of follow-up visits for monitoring and educated about the signs and symptoms of hepatotoxicity (371). For patients taking anti-TB and ART, the liver enzyme levels should be determined before initiation of therapy and closely monitored especially in the first three weeks of therapy. This can be achieved through directly observed therapy when applicable (365). If appropriate, monitoring of liver

enzymes should be continued for at least medication refilling visits with special attention to patients with malnutrition, pre-existing liver diseases and previous ADR history.

- Determining baseline body weight/BMI before initiation of the treatment, and throughout therapy. Dosing of each regimen should be individualised according to clinical condition and body weight. Furthermore, weight loss of 2 kg or more within 4 weeks during TB treatment is a risk factor for DIH (372). Therefore, the weight of patients taking anti-TB drugs should be measured at least at each visit for medication refilling and appropriate interventions should be considered when the patient is at risk for serious reactions. An adequate intake of nutrients is important for the integrity of liver metabolism and minimising the hepatotoxic effect of isoniazid and other anti-TB drugs, as the cytochrome P450 enzyme system is affected by malnourished states (373, 374).
- Pharmacovigilance/post-marketing surveillance should be integrated with the innovative community-based health extension program (254, 375) with a focus on clinic/home-based therapy observation especially for patients at risk of ADRs. This should be conducted under clinically trained pharmacists' supervision from primary (health centres and primary hospitals), secondary (general hospitals), and tertiary (specialised and referral hospitals) healthcare levels for patients using drugs for chronic diseases. All patients receiving drug therapy for chronic illnesses including TB/HIV should be linked with their respective village's health extension program for close monitoring, and referral (if potential ADRs suspected) for appropriate management. One option would be a scheduled regular home-based medication review process through health extension packages by clinically trained pharmacists. In addition, training and continuous supervision should be given to health extension workers on procedures to minimise the risk of complications by early assessment.

The main limitations of our study include lack of liver biopsy for diagnosing DIH. Causality in DIH is inherently difficult to prove, thus the diagnosis was a clinical one, based on a

consistent history and supporting laboratory data. Proving the diagnosis would require rechallenge with the suspected drug by the treating physician to see if a similar reaction recurred, however, this approach was not applied for some patients due to potentially severe deleterious outcomes and lack of guideline for re-initiation. We did not observe the progression of DIH to detect chronic DIH. Hepatotoxicity suspected to be caused by herbal remedies was not typically recorded due to the common practice of packaging multiple agents together, lack of dose standardisation, recall bias and impurity of products, which may have resulted in underestimation of the rate of DIH-related admissions. There was possible bias resulting from exclusion of some patients with hepatic encephalopathy that might be associated with severe DIH. As the study findings mainly depended on the patient characteristics and DIH detection methods, the results of this study should be generalised to other settings with caution. Despite its limitations, our study is important to clinicians and policy makers, as it revealed the anti-TB and ART drugs were commonly implicated in DIH-related hospitalisation and mortality for community-dwelling Ethiopian patients. Our study provided a detailed picture of clinical presentations and biochemical patterns due to its prospective methodology. In addition, we have identified low BMI, pre-existing liver disease, unintentional overdosing, and previous ADR history as risks for severe DIH; this suggests the need for education of both health professionals and patients to raise awareness of the need for early detection and initiation of suitable treatment to prevent complications or death. Our yearlong sampling in a teaching and referral hospital serving a population of 15 million avoided the bias associated with anti-infective use patterns due to seasonal variation.

5.6 Conclusion

DIH is an important cause of hospitalisation and mortality, with most cases cholestatic in biochemical pattern and caused by anti-TB drugs followed by ART. Special consideration

should be given to patients taking anti-TB and ART, particularly those who are underweight, with pre-existing liver disease, and a previous ADR history. Further prospective longitudinal studies with a large sample size should be conducted to assess the impact of infectious diseases (TB, HIV, and viral hepatitis), genetics, malnutrition, use of alcohol, and herbal remedies on rates of chronic progression and outcome prediction in patients with DIH.

Chapter Six

6. General discussion and conclusion

6.1 Principal findings

This thesis represents a substantial step forward for researchers in sub-Saharan Africa, including Ethiopia, on the burden of ADR-related hospital admissions and mortality, where such data are scarce. The thesis is comprised of a review and a significant prospective observational study with several analyses that provided several novel findings to add to the literature. The review revealed that the prevalence of ADR-related hospital admissions and mortality vary from 0.2% to 54.5% and 0.1% to 10.0%, respectively. The main findings from the prospective study were that the rates of ADR-related hospitalisation and mortality were 10.3% (or 3.4% of all medical admissions) and 1.5%, respectively. Drug-induced hepatotoxicity followed by acute kidney injury were the major ADRs implicated in both hospital admissions and mortality. Drugs commonly associated with both hospital admissions and mortality were anti-TB drugs followed by ART and cardiovascular agents. In addition, patients with lower body mass index, pre-existing renal and liver diseases, history of previous ADRs, multiple comorbidities and drugs were found to be independent predictors of ADR-related hospital admission with an area under the receiver operator curve of 79.0% (95% CI 73.9%-84.1%). Overall, the extent of ADR-related hospitalisation in adult patients was a substantial public health problem, with a significant number of fatal ADRs in patients presenting to hospital.

6.2 The burden of ADR-related hospital admissions and associated factors

ADRs were a common reason for hospital admission, with a substantial number of ADR-related deaths in patients presenting to hospital. Our review revealed that ADR-related hospital

admissions and mortality are a considerable burden to the adult population in both developed and developing countries, particularly in susceptible patient groups such as the elderly, patients with multiple comorbidities, and in developing countries, patients with HIV/AIDS taking ART. Our prospective study has also confirmed a comparable prevalence of ADR-related hospital admission and mortality in patients included in the study. Specifically, these findings were further augmented by comparable studies from developed (16, 30) and developing countries (35, 101) with regard to ADR-related hospital admissions. Similarly, ADR-related mortality was comparable to previously published studies that were conducted in South Africa (23), Iran (331) and India (64). It is clear that the burden of ADRs are an important public health problem demanding additional medical care irrespective of the differences in population socio-demographics, disease characteristics, drug therapy used, healthcare systems and, ethnic origins in both developing and developed countries.

The analyses conducted in this thesis found that the major ADRs suspected to be implicated in hospital admissions and deaths were DIH followed by AKI and electrolyte disorders, in contrast to ADRs reported from developed world, such as GI bleeding (99, 105), cardiovascular disorders (16, 30, 32, 93, 94) and electrolyte and metabolic disturbances (9, 16, 58, 94). In contrast to the findings from studies conducted in developed countries (10, 40), where the major causative agents were anticoagulants and cardiovascular agents, the drugs most commonly suspected of causing ADR-related hospital admissions and deaths were anti-TB and ART. This reflects the difference in disease distribution, population demographics, and drug therapy used between the study population in Ethiopia and developed countries. In addition, ADR-related hospital admissions and deaths occurred commonly in patients with various combinations of TB, HIV/AIDS, low BMI, and pre-existing liver diseases in contrast to the developed world cardiovascular diseases and cancers (9, 11, 17). There are multiple reasons behind these contrasting findings. These include the higher prevalence of concomitant

infectious diseases (TB or HIV or co-infection of both) and non-communicable chronic diseases, malnutrition, or as a consequence of HIV or TB, and use of multiple drugs with potential for interactions. Additionally, the presence of a substantial number of patients with pre-existing liver and kidney diseases might have increased the opportunity to derange pharmacokinetics, which might have led to drug interactions, serious ADRs, and finally death.

6.2.1 Anti-TB drug-related hospital admissions and mortality

Tuberculosis is a major public health problem in Ethiopia with the prevalence of 211 per 100,000 of the population, of whom 13% were HIV co-infected (300). TB is also a leading cause of morbidity, hospital admission and death in Ethiopia (376, 377). In this thesis, the prospective observational study found that anti-TB drugs, particularly isoniazid followed by pyrazinamide, were the major drugs implicated in ADR-related hospitalisation and mortality. Of 1,001 patients, 3.6% were admitted with anti-TB drug-related ADRs (mainly hepatotoxicity) and 0.7% died from anti-TB drug suspected ADRs. Of 207 TB infected patients included in this study, 61 (29.5%) were TB/HIV co-infected and taking concomitant anti-TB and antiretroviral therapies. Approximately one-third of these had ADRs, which is in-line with other studies (378, 379). Patients with advanced liver disease were at increased risk of developing ADRs, particularly in patients taking anti-TB drugs as was similarly found by Gaude et al. (380). Our findings revealed that underweight patients (<18.5kg/m^2) were at higher risk for ADR-related hospital admission and mortality than patients with normal weight. Previous studies revealed that malnutrition is a common health problem in developing countries including Ethiopia (196, 381) and important risk factor for ADR-related hospitalisation, especially in TB patients (162, 382, 383). Anti-TB induced hepatotoxicity is known to be an important reason for termination of anti-TB regimens (384) and prolongation of hospital stays with additional medical costs (385). ADRs due to first line anti-TB drugs are regarded as the major cause for non-adherence to TB and concomitant TB/HIV treatments

(386). At the same time, alternative agents may have higher complications with toxicity, and are often less effective. More importantly, ADRs due to anti-TB medication contribute to the prolongation of treatment duration, relapse of infection, drug resistance, treatment failure, and even death (387). In addition, anti-TB drug induced liver injury is a common cause for acute liver failure (133, 134), posing a challenge to the management of TB patients and TB control.

6.2.2 ART-related hospital admissions and mortality

The prevalence of HIV among the Ethiopian adult population was estimated to be 1.0% with national ART coverage of 52.0% (301). Following anti-TB agents, ART, particularly tenofovir, efavirenz and nevirapine, were the second most important group of agents implicated in ADR-related hospital admission and mortality. Overall, 2.2% of patients were admitted with ART-related ADRs and 0.6% of patients died from ART-related ADRs. There are a number of precipitating factors to this finding. These include the presence of larger number of patients taking relatively toxic agents, such as efavirenz and tenofovir in the ART regimen (388), a greater number of HIV patients who present with a complicated disease state (378, 389), and a larger number of patients with concomitant TB, HIV, and malnutrition with an immunocompromised state (389, 390). In addition, lack of continuous clinical/laboratory monitoring of drug therapy and skilled professionals at the follow-up clinics could have resulted in failure in early identification (or delay in diagnosis) of specific ADRs and hence increased ADR severity (270, 390, 391).

The presence of a larger number of patients with late clinical presentation of HIV or TB/HIV co-infection might have increased medical complexity, number of comorbidities (due to advanced and complicated AIDS stage) and medications used (392). In addition, the population in the study area is known to have higher than the country's average HIV prevalence (393), and worse health outcomes in many conditions over time (394), which may be precipitating

factors for the occurrence of more ART-related ADRs. For instance, out of 108 HIV/AIDS infected patients included in this study, 61 (56.5%) were classified as either WHO clinical stage III and IV. The main diagnoisis in patients presenting with clinical stage III were pulmonary TB and severe bacterial infections. The main diagnoisis in patients presented with clinical stage IV were extrapulmonary TB, Pneumocystis (jirovecii) pneumonia and extrapulmonary cryptococcal meningitis. Finally, all the above clinical conditions could have led to poor immune recovery and increased likelihood of ART-related ADRs (395). In line with our prospective study, previous studies have revealed that ART-related ADRs are the major reason for modification and/or discontinuation of therapy (388, 396), hospitalisation (23, 101), life threatening reactions demanding intensive care (397), and mortality (65). ADRs associated with ART have thus become the most important limiting factor to the successful treatment of HIV and other opportunistic infections in community dwelling patients on chronic drug treatment follow up, especially in developing countries (398, 399).

6.3 Research implications

There are multiple strategies for preventing ADR-related hospitalisation and the associated burden described in the literature. Some of these include focusing on the patient care process using different intervention strategies, such as pharmacy-led interventions (230), monitoring ongoing drug therapy (225), preventing drug interactions (222), and highlighting the patients at high risk for ADRs (213). Highlighting the patients at high risk for ADRs depends on several factors, such as the disease characteristics and population demographics (9, 14, 23, 100), complexity of diseases and medications prescribed (9, 14, 94), healthcare systems (104), and ethnic origin (168, 250) of the study population. Medical practitioners often lack awareness of factors contributing to ADR-related hospitalisations (251, 252). To overcome this, identification and reporting of factors contributing to ADR-related hospitalisation for community-based patients is crucial to develop preventive strategies to decrease the burden

(199, 200). Studies, mainly from developed countries (9, 14), have identified several predictors of ADR-related hospital admissions, however, there is scanty data in the developing countries including Ethiopia. Hence, we identified six independent predictors of ADR-related hospital admission with a fair to good predicting capacity of 79.0% (Figure 3.1), although these predictors were not validated in similar or other populations. The sensitivity and specificity of the ADR risk prediction in AUROC were 59.2% and 86.6%, respectively, suggesting that it could moderately rule-in patients at risk of ADRs and strongly rule-out those patients not at risk of ADRs, respectively. This was further augmented by an ADR preventability assessment using Schumock and Thornton's preventability assessment criteria, in which the majority of the ADR-related hospitalisations were preventable provided these risk factors were reviewed and monitored closely. This is, therefore, a novel finding in developing countries including Ethiopia, suggesting a higher burden of malnutrition and rising prevalence of chronic illnesses, such as renal and liver diseases demanding multiple medications. In addition, the study will reinvigorate medical practitioners in enhancing early identification of patients at higher risk for ADRs, promote safe and rational use of medicines through consideration of dosage regimen individualisation, and close monitoring.

The vast majority of cases of ADR-related hospital admission and mortality were preventable based on Schumock and Thornton criteria (201). Most of the ADRs identified were type A (pharmacologically predictable or dose-related), and resulted from an exaggeration of a drug's normal pharmacological action when given in the usual therapeutic dose. The majority of ADRs, therefore, are well known prior to product authorisation and are listed in product labelling. More importantly, some dose-related ADRs may reflect a lack of knowledge about pharmacokinetics and pharmacodynamics in patients with malnutrition, renal and liver diseases, who constituted a substantial number of patients; these risk factors were reported to be independent predictors for ADR-related hospital admission. The pathophysiology of

malnutrition in adults has not been studied in detail; however, available limited studies (400, 401) have shown that medical conditions, such as HIV, TB, renal and liver disease are important precipitating factors that need special focus. In addition, use of isoniazid in malnourished patients increases susceptibility to ADRs due to increased formation of toxic metabolites (370) and depletion of glutathione stores that increases vulnerability to oxidative liver injury (368). In general, the high proportion of preventable ADRs highlights the importance of improving medication use, particularly in vulnerable patient groups, such as patients with renal and liver diseases, TB/HIV, and malnutrition.

In this thesis, overall findings highlight the need to focus on pre-treatment evaluation of community dwelling patients, particularly patients with TB/HIV co-infection taking concomitant anti-TB drugs and ART, pre-existing renal and liver disease, and malnutrition, in order to reduce drug-related adverse outcomes including death. Our findings and the limited related literature (354-356) suggest that this pre-treatment evaluation should include, but not be limited to, implementation of practical aspects of a multidisciplinary care approach that focus on screening for pre-existing renal and liver disease and nutritional status and assessment of the benefit of empirical treatment initiation versus the risk of adverse outcomes. This should be followed by patient monitoring, adherence to existing treatment protocols, improving of patient education, strengthening of clinic/home-based directly observed therapy, and the health extension program in the case of Ethiopia. Patients should be closely monitored in a multidisciplinary team approach during their treatment follow-up period and linked with their respective village's health extension program for continuous monitoring, and referral (if potential ADRs suspected) for appropriate management. One component of continuous patient monitoring would be implementing a scheduled regular home-based medication review process through health extension packages by clinically trained pharmacists. In addition, continuous

training and supervision should be given to health extension workers on procedures of early assessment to reduce ADR-related complications.

The findings of this thesis are relevant to healthcare authorities, program leaders, policy makers, and researchers as the series of analyses have revealed several important findings regarding ADR-related hospital admission and mortality in sub-Saharan Africa in general and Ethiopia in particular, where there is scanty data. The results will aid policy makers and healthcare system managers to develop efficient strategies to reduce the burden of ADR-related hospital admission on the healthcare system. The results will encourage pharmaceutical regulatory authorities to implement pharmacovigilance/post-marketing surveillance in routine clinical practice in different healthcare levels. The findings of this thesis also encourage a multidisciplinary team approach with the involvement of clinically trained pharmacists in the direct patient care process. As an epidemiological study, it identified ADR as an important public health problem causing significant morbidity, hospital admissions and deaths, so this could encourage researchers to consider multicentre longitudinal studies with interventional strategies to identify root causes of ADRs and reduce the ADR-related burden.

6.4 Strengths and limitations

The use of recognised and previously published criteria for assessment of ADR causality, type, severity, and preventability might increase the robustness of the method employed in the current study. Yet there is no universally accepted method for ADR assessment, as there is still ongoing debate and no consensus among researchers and regulatory authorities (402). Consequently, this might have led to over/under-estimation of the burden of ADRs. We used a three-step process to assess ADR causality, type, severity, and preventability; evaluating individual patient's clinical and laboratory parameters with regard to suspected ADR(s), using previously recognised methods (Naranjo ADR algorithm, Rawlins and Thompson

classification, modified Hartwig et al. severity scale and Schumock and Thornton preventability criteria) followed by consensus review between experts. Therefore, use of these mixed approaches helped mitigate the subjectivity associated with interpretation of the causality, type, severity, and preventability of the ADRs and further increased the robustness of the results. Previous researchers (116, 213) have applied a similar approach. The adoption of the widely used WHO definition of ADR (21) has enabled direct comparisons with multiple studies.

Most importantly, our study provided a detailed picture of clinical presentations, sociodemographic and biochemical patterns of each case due to its prospective methodology. The prospective identification of ADRs immediately upon admission by clinical experts has allowed for relatively accurate estimation of the problem in the study setting. Our yearlong sampling in a teaching and referral hospital serving a population of 15 million avoided the bias associated with anti-infective use patterns due to seasonal variation. Our study is important to clinicians and policy makers, as it revealed the anti-TB and ART drugs were commonly implicated in ADR-related hospitalisation and mortality for community-dwelling Ethiopian patients. In addition, we have identified several risk factors for ADR-related hospital admissions and mortality, suggesting the need for education of both health professionals and patients to raise awareness of the need for early detection and initiation of suitable treatment to prevent complications or death.

There are several limitations in this work. These limitations could inform researchers and medical practitioners in the area of medication safety to improve planning of future studies in order to maximise the generalisability and validity of the findings. Due to logistic and time limitations, our study was conducted only in one centre so may lack direct generalisability to other settings.

ADR causality assessment is inherently difficult, thus the diagnosis was a clinical one, based on a consistent history and supporting laboratory data. For instance, there was lack of liver biopsy for diagnosing DIH. Proving the diagnosis of ADRs would require rechallenge with the suspected drug by the treating physician to see if a similar reaction recurred, however, this approach was not applied for some patients due to potentially severe deleterious outcomes and lack of guidelines for re-initiation. We did not observe the progression of ADRs to detect chronic ADRs due to the nature of the study. ADRs suspected to be caused by commonly used over-the-counter medicines, contraceptives, topical agents, and herbal remedies were not commonly recorded in detail in drug histories, which may have resulted in underestimation of the true rate of ADR-related admissions. A large number of patients were excluded from the study due to their inability to be interviewed as a result of health or other reasons which may have also resulted in underestimation of the true rate of ADR-related admissions. The characteristics (socio-demographic and clinical conditions) of the excluded patients were not collected in the current study, which might be an important potential source of bias for readers who want to differentiate these group of patients from the study patients. Additionally, patients may have died due to ADRs prior to hospital admission, resulting in underestimation of the true ADR-related death rate. As the study findings mainly depended on the patient demographics, pre-existing diseases characteristics, drug therapy used and ADR detection methods, the results of this study should be generalised to other settings with caution.

Another limitation of the current work was the inability to measure ADR-related economic impact on the healthcare system and individual patient as part of the outcomes of the study. The estimation of ADR-related costs would help strengthen the argument to support the implementation of the intervention strategies through a reasonable prioritisation, which could help reduce the overall costs. Therefore, future work in this area will need specific evaluation to quantify both direct and indirect costs of ADRs on patients and the healthcare system, which

could allow us to fully understand the economic impact of interventions aimed at reducing harm due to ADRs.

6.5 Future research directions

More research is needed into intervention strategies to help reduce ADR-related hospitalisation and mortality. However, key areas that demand urgent interventions based on our study findings include patients taking anti-TB drugs (isoniazid and pyrazinamide) and ART (tenofovir, efavirenz and nevirapine), with a special focus on patients with malnutrition, previous ADR history, and pre-existing renal and liver diseases. Patients with cardiovascular disorders taking furosemide, enalapril, atorvastatin, warfarin and heparin also require special consideration. Given our findings that the majority of events occurred in patients receiving treatment for chronic infectious and non-communicable diseases, ADR risk assessment and intervention strategies should focus on these groups of patients to minimise the occurrence of preventable ADR-related hospitalisation and mortality in Ethiopia, noting that measuring the effectiveness of such interventions is an area requiring further research.

In summary, this thesis has provided the most robust estimate of the extent and nature of the burden of ADR-related hospital admission and mortality in Ethiopian patients. Given the overburdening of the growing healthcare system with ADR-related hospitalisation and mortality, urgent work is required to:

- investigate the impact of genetics, malnutrition, and chronic infectious and non-communicable diseases on the acquisition and outcomes of ADRs;
- develop robust methods for prevention of the occurrence of ADRs in the future;
- validate the ADR risk predictors and, if valid, implement these in practice; and

- evaluate the impact of ADR prevention strategies with the ultimate goal of preventing or reducing the risk of acquiring ADRs, improving patient outcomes, and minimising ADR-related costs to the healthcare system.

Considering the significant problem of ADR-related admission and mortality and lack of universally accepted standardised methods for assessing ADR causality, type, severity, and preventability, there is a need to develop robust standardised methods in order to accurately estimate the worldwide epidemiology and financial costs of the problem to the health care system.

6.6 Thesis conclusion

Our study provided several novel findings regarding hospitalisation and mortality related to ADRs in Ethiopian patients. Our work revealed that the extent of ADR-related hospitalisation in adults is an important public health problem, with a significant number of fatal ADRs in patients presenting to hospital. Well-known reactions to commonly used drugs, such as anti-TB drugs, ART and cardiovascular agents, are the most frequently occurring ADRs in patients presenting to hospital, suggesting that strategies for their prevention should be identifiable. The ADR-related hospitalisation risk prediction demonstrated some ability to identify patients at higher risk for ADRs, such as patients with a lower BMI, previous ADR history, renal and liver diseases, and multiple comorbidities and medications. Therefore, consideration of these risk factors by medical practitioners during assessment of patients at emergency and chronic care centres might help distinguish patients who are at higher risk of ADR-related hospitalisation. Healthcare professionals, particularly physicians, pharmacists, and nurses should work more effectively as a multidisciplinary team to identify, prevent, and manage the ADR-related burden experienced by patients.

References

1. Pugatch M, Torstensson D, Laufer M. The evolution of pharmacovigilance - Pugatch consilium:Labeling, packaging and pharmacopeia standards: Novartis Pharmaceuticals Corporation 2015. Via http://www.pugatch-consilium.com/reports/The%20Evolution%20of%20Pharmacovigilance.pdf.

2. Sammons HM, Choonara I. Clinical trials of medication in children, 1996-2002. *European Journal of Clinical Pharmacology.* 2005;61(2):165-7. doi:10.1007/s00228-005-0894-9.

3. Gallagher RM, Mason JR, Bird KA, et al. Adverse drug reactions causing admission to a paediatric hospital. *PLoS One*. 2012;7 (12):e50127. doi:10.1371/journal.pone.0050127

4. McBride WG. Teratogenic action of thalidomide. *Lancet.* 1978;1(8078):1362.

5. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *Journal of American Medical Association.* 2001;286 (8):954-9.

6. World Health Organization. Safety monitoring of medicinal products: Guidelines for setting up and running a pharmacovigilance centre. Uppsala: *Uppsala Monitoring Centre, World Health Organization;* 2000.

7. Levy M, Kewitz H, Altwein W, Hillebrand J, Eliakim M. Hospital admissions due to adverse drug reactions: A comparative study from Jerusalem and Berlin. *European Journal of Clinical Pharmacology.* 1980;17(1):25-31.

8. Levy M, Lipshitz M, Eliakim M. Hospital admissions due to adverse drug reactions. *The American Journal of the Medical Sciences.* 1979;277 (1):49-56.

9. Onder G, Pedone C, Landi F, et al. Adverse drug reactions as cause of hospital admissions: Results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA). *Journal of the American Geriatrics Society.* 2002;50(12):1962-8.

10. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18 820 patients. *British Medical Journal.* 2004;329(7456):15-9.

11. Van der Hooft CS, Dieleman JP, Siemes C, et al. Adverse drug reaction-related hospitalisations: A population-based cohort study. *Pharmacoepidemiology and Drug Safety.* 2008;17(4):365-71.

12. Van der Hooft CS, Sturkenboom MC, Van Grootheest K, Kingma HJ, Stricker BH. Adverse drug reaction-related hospitalisations: A nationwide study in The Netherlands. *Drug Safety.* 2006;29(2):161-8.

13. Varallo FR, Capucho HC, Planeta CS, Mastroianni PC. Possible adverse drug events leading to hospital admission in a Brazilian teaching hospital. *Clinics.* 2014;69(3):163-7. doi:10.6061/clinics/2014(03)03

14. Zopf Y, Rabe C, Neubert A, Hahn EG, Dormann H. Risk factors associated with adverse drug reactions following hospital admission: A prospective analysis of 907 patients in two German university hospitals. *Drug Safety*. 2008;31(9):789-98.

15. Carrasco-Garrido P, de Andres LA, Barrera VH, de Miguel GA, Jimenez-Garcia R. Trends of adverse drug reactions related-hospitalizations in Spain (2001-2006). *BMC Health Services Research.* 2010;10:287. doi:10.1186/1472-6963-10-287.

16. Alexopoulou A, Dourakis SP, Mantzoukis D, et al. Adverse drug reactions as a cause of hospital admissions: A 6-month experience in a single center in Greece. *European Journal of Internal Medicine.* 2008;19(7):505-10. doi:10.1016/j.ejim.2007.06.030.

17. Patel H, Bell D, Molokhia M, et al. Trends in hospital admissions for adverse drug reactions in England: Analysis of national hospital episode statistics 1998-2005. *BMC Clinical Pharmacology*. 2007;7:9. doi:10.1186/1472-6904-7-9.

18. Moore N, Lecointre D, Noblet C, Mabille M. Frequency and cost of serious adverse drug reactions in a department of general medicine. *British Journal of Clinical Pharmacology.* 1998;45(3):301-8.

19. Roughead EE, Gilbert AL, Primrose JG, Sansom LN. Drug-related hospital admissions: a review of Australian studies published 1988-1996. *The Medical Journal of Australia.* 1998;168(8):405-8.

20. Pouyanne P, Haramburu F, Imbs JL, Begaud B. Admissions to hospital caused by adverse drug reactions: Cross sectional incidence study. French Pharmacovigilance Centres. *British Medical Journal.* 2000;320(7241):1036.

21. World Health Organisation. International drug monitoring: The role of national centres. Report of a World Health Organisation meeting. *World Health Organization technical report series.* 1972;498:1-25.

22. Angamo MT, Chalmers L, Curtain CM, Bereznicki LR. Adverse-Drug-Reaction-Related Hospitalisations in Developed and Developing Countries: A Review of Prevalence and Contributing Factors. *Drug Safety.* 2016;39(9):847-57. doi:10.1007/s40264-016-0444-7.

23. Mehta U, Durrheim DN, Blockman M, Kredo T, Gounden R, Barnes KI. Adverse drug reactions in adult medical inpatients in a South African hospital serving a community with a high HIV/AIDS prevalence: Prospective observational study. *British Journal of Clinical Pharmacology*. 2008;65(3):396-406. doi:10.1111/j.1365-2125.2007.03034.x.

24. Edwards IR, Aronson JK. Adverse drug reactions: Definitions, diagnosis, and management. *The Lancet.* 2000;356(9237):1255-9. doi:10.1016/s0140-6736(00)02799-9

25. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: A clinician's guide to terminology, documentation, and reporting. *Annals of Internal Medicine.* 2004;140(10):795-801.

26. National Coordinating Council (NCC) for Medication Error Reporting and Prevention (MERP). via http://www.ihi.org/resources/Pages/OtherWebsites/NCCMERP.aspx. Accessed on Oct 2018.

27. Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: Detection and classification methods. *Quality & Safety in Health Care*. 2004;13(4):306-14. doi:10.1136/qhc.13.4.306.

28. Sonal Sekhar M, Adheena Mary C, Anju PG, Hamsa NA. Study on drug related hospital admissions in a tertiary care hospital in South India. *Saudi Pharmaceutical Journal : SPJ : The Official Publication of the Saudi Pharmaceutical Society.* 2011;19(4):273-8. doi:10.1016/j.jsps.2011.04.004.

29. Varallo FR, Lima MFR, Galduroz JCF, Mastroianni PC. Adverse drug reaction as cause of hospital admission of elderly people: A Pilot study. *Latin American Journal of Pharmacy.* 2011;30(2):347-53.

30. Ahern F, Sahm LJ, Lynch D, McCarthy S. Determining the frequency and preventability of adverse drug reaction-related admissions to an Irish University Hospital: A cross-sectional study. *Emergency Medicine Journal : EMJ.* 2014;31(1):24-9. doi:10.1136/emermed-2012-201945.

31. Franceschi M, Scarcelli C, Niro V, et al. Prevalence, clinical features and avoidability of adverse drug reactions as cause of admission to a geriatric unit: A prospective study of 1756 patients. *Drug Safety.* 2008;31(6):545-56.

32. Green CF, Mottram DR, Rowe PH, Pirmohamed M. Adverse drug reactions as a cause of admission to an acute medical assessment unit: A pilot study. *Journal of Clinical Pharmacy and Therapeutics.* 2000;25(5):355-61.

33. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. *Annals of Pharmacotherapy.* 2002;36(9):1331-6.

34. Patel KJ, Kedia MS, Bajpai D, Mehta SS, Kshirsagar NA, Gogtay NJ. Evaluation of the prevalence and economic burden of adverse drug reactions presenting to the medical emergency department of a tertiary referral centre: A prospective study. *BMC Clinical Pharmacology.* 2007;7:8. doi:10.1186/1472-6904-7-8.

35. Alvarez PA, Bril F, Castro V, et al. Adverse drug reactions as a reason for admission to an internal medicine ward in Argentina. *The International Journal of Risk & Safety in Medicine.* 2013;25(3):185-92. doi:10.3233/jrs-130596.

36. Shepherd G, Mohorn P, Yacoub K, May DW. Adverse drug reaction deaths reported in United States vital statistics, 1999-2006. *Annals of Pharmacotherapy.* 2012;46(2):169-75. doi:10.1345/aph.1P592.

37. Chen YC, Fan JS, Hsu TF, et al. Detection of patients presenting with adverse drug events in the emergency department. *Internal Medicine Journal.* 2012;42(6):651-7. doi:10.1111/j.1445-5994.2011.02684.x.

38. Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK. Adverse drug reactions. *British Medical Journal.*1998;316(7140):1295-8.

39. Brvar M, Fokter N, Bunc M, Mozina M. The frequency of adverse drug reaction related admissions according to method of detection, admission urgency and medical department specialty. *BMC Clinical Pharmacology.* 2009;9:8. doi:10.1186/1472-6904-9-8.

40. Wester K, Jönsson AK, Spigset O, Druid H, Hägg S. Incidence of fatal adverse drug reactions: A population based study. *British Journal of Clinical Pharmacology.* 2008;65(4):573-9.

41. Davies EC, Green CF, Mottram DR, Rowe PH, Pirmohamed M. Emergency re-admissions to hospital due to adverse drug reactions within 1 year of the index admission. *British Journal of Clinical Pharmacology.* 2010;70(5):749-55. doi:10.1111/j.1365-2125.2010.03751.x.

42. Ramesh M, Pandit J, Parthasarathi G. Adverse drug reactions in a south Indian hospital--their severity and cost involved. *Pharmacoepidemiology and Drug Safety.* 2003;12(8):687-92. doi:10.1002/pds.871.

43. Pouyanne P, Haramburu F, Imbs JL, Bégaud B. Admissions to hospital caused by adverse drug reactions: Cross sectional incidence study. *British Medical Jounal*. 2000;320(7241):1036.

44. Jones JK. Adverse drug reactions in the community health setting: Approaches to recognizing, counseling, and reporting. *Family & Community Health.* 1982;5(2):58-67.

45. Dormann H, Muth-Selbach U, Krebs S, et al. Incidence and costs of adverse drug reactions during hospitalisation : Computerised monitoring versus stimulated spontaneous reporting. *Drug Safety.* 2000;22(2):161-8. doi:10.2165/00002018-200022020-00007.

46. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *American Journal of Hospital Pharmacy. 1992*;49(9):2229-32.

47. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: A prospective analysis of 3695 patient-episodes. *PLoS One*. 2009;4(2):e4439.

48. Padmavathi S, Manimekalai K, Ambujam S. Causality, severity and preventability assessment of adverse cutaneous drug reaction: A prospective observational study in a tertiary care hospital. *Journal of Clinical and Diagnostic Research : JCDR*. 2013;7(12):2765-7. doi:10.7860/jcdr/2013/7430.3753

49. Arulmani R, Rajendran S, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. *British Journal of Clinical Pharmacology*. 2008;65(2):210-6.

50. Calderon-Ospina C, Bustamante-Rojas C. The DoTS classification is a useful way to classify adverse drug reactions: A preliminary study in hospitalized patients. *The International Journal of Pharmacy Practice.* 2010;18(4):230-5. doi:10.1111/j.2042-7174.2010.00039.x.

51. Lobo MG, Pinheiro SM, Castro JG, Momente VG, Pranchevicius MC. Adverse drug reaction monitoring: Support for pharmacovigilance at a tertiary care hospital in Northern Brazil. *BMC Pharmacology & Toxicology.* 2013;14:5. doi:10.1186/2050-6511-14-5.

52. Mannesse CK, Derkx FH, de Ridder MA, Man in 't Veld AJ, van der Cammen TJ. Contribution of adverse drug reactions to hospital admission of older patients. *Age and Ageing.* 2000;29(1):35-9.

53. Mohebbi N, Shalviri G, Salarifar M, Salamzadeh J, Gholami K. Adverse drug reactions induced by cardiovascular drugs in cardiovascular care unit patients. *Pharmacoepidemiology and Drug Safety.* 2010;19(9):889-94. doi:10.1002/pds.1916.

54. Ponte ML, Ragusa M, Armenteros C, Wachs A. Importance of pharmacovigilance in current medical practice. *Medicina.* 2013;73(1):35-8.

55. Pourseyed S, Fattahi F, Pourpak Z, et al. Adverse drug reactions in patients in an Iranian department of internal medicine. *Pharmacoepidemiology and Drug Safety.* 2009;18(2):104-10. doi:10.1002/pds.1663.

56. Wiffen P, Gill M, Edwards J, Moore A. Adverse drug reactions in hospital patients. A systematic review of the prospective and retrospective studies. *Bandolier Extra.* 2002:1-15.

57. Burgess CL, Holman CD, Satti AG. Adverse drug reactions in older Australians, 1981-2002. *The Medical Journal of Australia.* 2005;182(6):267-70.

58. Rottenkolber D, Schmiedl S, Rottenkolber M, et al. Adverse drug reactions in Germany: direct costs of internal medicine hospitalizations. *Pharmacoepidemiology and Drug Safety.* 2011;20(6):626-34. doi:10.1002/pds.2118.

59. Byrne DW, France DJ, Johnston PE, et al. Assessment of adverse drug events among patients in a tertiary care medical center. American Journal of Health System Pharmacists . 2006;63 (22): 2218-27.

60. Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States in years 1970-2002. *Journal of the American Medical Association*. 2005;294:1255-9.

61. Hodgkinson MR, Dirnbauer NJ, Larmour I. Identification of adverse drug reactions using the ICD-10 Australian Modification Clinical Coding Surveillance. *Journal of Pharmacy Practice and Research.* 2009;39(1):19-23.

62. Zoppi M, Braunschweig S, Kuenzi UP, Maibach R, Hoigne R. Incidence of lethal adverse drug reactions in the comprehensive hospital drug monitoring, a 20-year survey, 1974-1993, based on the data of Berne/St. Gallen. *European Journal of Clinical Pharmacology.* 2000;56(5):427-30.

63. Juntti-Patinen L, Neuvonen PJ. Drug-related deaths in a university central hospital. *European Journal of Clinical Pharmacology.* 2002;58(7):479-82. doi:10.1007/s00228-002-0501-2.

64. Vora MB, Trivedi HR, Shah BK, Tripathi CB. Adverse drug reactions in inpatients of internal medicine wards at a tertiary care hospital: A prospective cohort study. *Journal Of Pharmacology & Pharmacotherapeutics.* 2011;2(1):21-5. doi:10.4103/0976-500x.77102.

65. Mouton JP, Mehta U, Parrish AG, et al. Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: A cross-sectional survey. *British Journal of Clinical Pharmacology.* 2015;80(4):818-26. doi:10.1111/bcp.12567.

66. Noblat AC, Noblat LA, Toledo LA, et al. Prevalence of hospital admission due to adverse drug reaction in Salvador, Bahia. *Revista da Associacao Medica Brasileira (1992).* 2011;57(1):42-5.

67. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *Journal of the American Medical Association.* 1997;277(4):301-6.

68. Wu C, Bell CM, Wodchis WP. Incidence and economic burden of adverse drug reactions among elderly patients in Ontario emergency departments: A retrospective study. *Drug Safety.* 2012;35(9):769-81. doi:10.2165/11599540-000000000-00000.

69. Breckenridge A. The burden of adverse drug events. *British Journal of Clinical Pharmacology.* 2015;80(4):785-7. doi:10.1111/bcp.12507.

70. Rothschild JM, Federico FA, Gandhi TK, Kaushal R, Williams DH, Bates DW. Analysis of medication-related malpractice claims: Causes, preventability, and costs. *Archives of Internal Medicine. 2002*;162(21):2414-20.

71. Studdert DM, Thomas EJ, Burstin HR, Zbar BI, Orav EJ, Brennan TA. Negligent care and malpractice claiming behavior in Utah and Colorado. *Medical Care.* 2000;38(3):250-60.

72. Anderson JA, Adkinson NF, Jr. Allergic reactions to drugs and biologic agents. *Journal of the American Medical Association.* 1987;258(20):2891-9.

73. deShazo RD, Kemp SF. Allergic reactions to drugs and biologic agents. *Journal of the American Medical Association*. 1997;278(22):1895-906.

74. Executive summary of disease management of drug hypersensitivity: A practice parameter. Joint task force on practice parameters, the american academy of allergy, asthma

and immunology, and the joint council of allergy, asthma and immunology. *Annals of Allergy, Asthma and Immunology.* 1999;83:665–700. Via https://www.ncbi.nlm.nih.gov/pubmed/10616910.

75. Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, ed. Textbook of adverse drug reactions, 2nd edn. *Oxford: Oxford University Press*. 1981:11.

76. von Euler M, Eliasson E, Ohlen G, Bergman U. Adverse drug reactions causing hospitalization can be monitored from computerized medical records and thereby indicate the quality of drug utilization. *Pharmacoepidemiology and Drug Safety.* 2006;15(3):179-84. doi:10.1002/pds.1154.

77. Tribin˜o G, Maldonado C, Segura O, Dı´az J. Direct costs and clinical aspects of adverse drug reactions in patients admitted to a level 3 hospital internal medicine ward. *Biomedica.* 2006;26:31-41.

78. Rawlins MD. Pharmacovigilance: paradise lost, regained or postponed? The William Withering Lecture 1994. *Journal of the Royal College of Physicians of London*. 1995;29(1):41-9.

79. Aronson JK. Drug therapy. In: Haslett C, Chilvers ER, Boon NA, Colledge NR, Jaa H, editors. Davidson's principles and practice of medicine. 19th ed ed. Edinburgh: Elsevier Science; 2002.

80. Aronson JK, Ferner RE. Joining the DoTS: New approach to classifying adverse drug reactions. *British Medical Journal.* 2003;327(7425):1222-5. doi:10.1136/bmj.327.7425.1222.

81. Zaki SA. Adverse drug reaction and causality assessment scales. *Lung India : Official organ of Indian Chest Society*. 2011;28(2):152-3. doi:10.4103/0970-2113.80343.

82. Gaurav Chhabra. Causality assessment,methods,pharmacovigilance: UIPS, *Panjab University (Pharmacology)* 2017.

83. Hutchinson TA, Lane DA. Standardized methods of causality assessment for suspected adverse drug reactions. *Journal of Chronic Diseases.* 1986;39(11):857-60.

84. World Health Organisation. The use of the WHO-UMC system for standardised case causality assessment via http://who-umc.org/Graphics/24734.pdf.

85. Irey NS. Teaching monograph. Tissue reactions to drugs. *The American Journal of Pathology*. 1976;82(3):613-47.

86. Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. Clinical Pharmacology and Therapeutics. 1977;21(3):247-54.

87. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. Background, description, and instructions for use. *Journal of American Medical Association.* 1979;242(7):623-32.

88. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology and Therapeutics.* 1981;30(2):239-45.

89. Khan LM, Al-Harthi SE, Osman AM, Sattar MA, Ali AS. Dilemmas of the causality assessment tools in the diagnosis of adverse drug reactions. *Saudi Pharmaceutical Journal: SPJ : The Official Publication of the Saudi Pharmaceutical Society.* 2016;24(4):485-93. doi:10.1016/j.jsps.2015.01.010

90. Busto U, Naranjo CA, Sellers EM. Comparison of two recently published algorithms for assessing the probability of adverse drug reactions. *British Journal of Clinical Pharmacology.* 1982;13(2):223-7.

91. Lanctot KL, Naranjo CA. Comparison of the Bayesian approach and a simple algorithm for assessment of adverse drug events. *Clinical Pharmacology and Therapeutics*. 1995;58(6):692-8. doi:10.1016/0009-9236(95)90026-8

92. Routledge P. A. Adverse drug reactions and interactions: Mechanisms, risk factors, detection, management and prevention. In: John Talbot., Waller. P, editors. Stephens' detection of new adverse drug reactions 5th ed: John Wiley & Sons, Ltd.; 2004.

93. Franceschi M, Scarcelli C, Niro V, et al. Prevalence, clinical features and avoidability of adverse drug reactions as cause of admission to a Geriatric Unit: A prospective study of 1756 patients. *Drug Safety.* 2008;31(6):545-56. doi:10.2165/00002018-200831060-00009.

94. Hofer-Dueckelmann C, Prinz E, Beindl W, et al. Adverse drug reactions (ADRs) associated with hospital admissions : Elderly female patients are at highest risk. *International Journal of Clinical Pharmacology and Therapeutics.* 2011;49(10):577-86.

95. Hopf Y, Watson M, Williams D. Adverse-drug-reaction related admissions to a hospital in Scotland. *Pharmacy World Science.* 2008;30(6):854-62. doi:10.1007/s11096-008-9240-5.

96. Olivier P, Bertrand L, Tubery M, Lauque D, Montastruc JL, Lapeyre-Mestre M. Hospitalizations because of adverse drug reactions in elderly patients admitted through the emergency department: A prospective survey. *Drugs & Aging.* 2009;26(6):475-82. doi:10.2165/00002512-200926060-00004.

97. Ruiter R, Visser LE, Rodenburg EM, Trifiro G, Ziere G, Stricker BH. Adverse drug reaction-related hospitalizations in persons aged 55 years and over: A population-based study in the Netherlands. *Drugs & Aging.* 2012;29(3):225-32. doi:10.2165/11599430-000000000-00000.

98. Pedros C, Quintana B, Rebolledo M, Porta N, Vallano A, Arnau JM. Prevalence, risk factors and main features of adverse drug reactions leading to hospital admission. *European Journal of Clinical Pharmacology*. 2014;70(3):361-7. doi:10.1007/s00228-013-1630-5.

99. van der Hooft CS, Dieleman JP, Siemes C, et al. Adverse drug reaction-related hospitalisations: A population-based cohort study. *Pharmacoepidemiology and Drug Safety*. 2008;17(4):365-71.

100. Sánchez Muñoz-Torrero JF, Barquilla P, Velasco R, et al. Adverse drug reactions in internal medicine units and associated risk factors. *European Journal of Clinical Pharmacology*. 2010;66(12):1257-64.

101. Mouton JP, Njuguna C, Kramer N, et al. Adverse Drug Reactions Causing Admission to Medical Wards: A Cross-Sectional Survey at 4 Hospitals in South Africa. *Medicine.* 2016;95(19):e3437. doi:10.1097/md.0000000000003437.

102. Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. *Annals of Internal Medicine*. 2007;147(11):755-65.

103. Hartholt KA, van der Velde N, Looman CW, et al. Adverse drug reactions related hospital admissions in persons aged 60 years and over, The Netherlands, 1981-2007: Less rapid increase, different drugs. *PLoS One.* 2010;5(11):e13977. doi:10.1371/journal.pone.0013977.

104. Perez Menendez-Conde C, Bermejo Vicedo T, Delgado Silveira E, Carretero Accame E. Adverse drug reactions which provoke hospital admission. *Farmacia Hospitalaria : Organo Oficial De Expresion Cientifica De La Sociedad Espanola De Farmacia Hospitalaria.* 2011;35(5):236-43. doi:10.1016/j.farma.2010.08.003.

105. Schneeweiss S, Hasford J, Gottler M, Hoffmann A, Riethling AK, Avorn J. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: A longitudinal population-based study. *European Journal of Clinical Pharmacology*. 2002;58(4):285-91. doi:10.1007/s00228-002-0467-0.

106. Lazarou J, Pomeranz B, Corey P. Incidence of Adverse drug reactions in hospitalised patients. A Meta-analysis of prospective studies. *Journal of the American Medical Association.* 1998;279(15):1200-5.

107. Varallo FR, Capucho HC, Planeta CD, Mastroianni PD. Possible adverse drug events leading to hospital admission in a Brazilian teaching hospital. *Clinics.* 2014;69(3):163-7. doi:10.6061/clinics/2014(03)03.

108. Walsh D, Lavan A, Cushing AM, Williams D. Adverse drug reactions as a cause of admission to a University Teaching Hospital. *Irish Journal of Medical Science.* 2013;182:S282-S.

109. Tipping B, Kalula S, Badri M. The burden and risk factors for adverse drug events in older patients: A prospective cross-sectional study. *South African medical journal = Suid-Afrikaanse Tydskrif vir Geneeskunde.* 2006;96(12):1255-9.

110. National Board of Health, theme report 2007: *Risikomedicin, Copenhagen,* 2007. Via https://laegemiddelstyrelsen.dk/en/publications/2007/publication-on-medicines-most-frequently-involved-in-serious-adverse-drug-events/~/media/D351DCAA2DB4463498724643F4E876C6.ashx.

111. The Danish medicines agency's prevention of medication errors' network. report on medicines most frequently involved in serious adverse drug events by high-alert medicines'

working group 2008-10. *Copenhagen: The Danish Medicines Agency's Prevention of Medication Errors Network*. 2011.

112. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *The New England Journal of Medicine.* 2003;348(16):1556-64. doi:10.1056/NEJMsa020703.

113. Mens H, Katzenstein TL. Hepatic failure due to nevirapine treatment for HIV infection. *Ugeskrift for Laeger.* 2005;167(46):4359.

114. Jha AK, Kuperman GJ, Rittenberg E, Teich JM, Bates DW. Identifying hospital admissions due to adverse drug events using a computer-based monitor. *Pharmacoepidemiology and Drug Safety.* 2001;10(2):113-9. doi:10.1002/pds.568.

115. Hallas J, Worm J, Beck-Nielsen J, et al. Drug related events and drug utilization in patients admitted to a geriatric hospital department. *Danish Medical Bulletin.* 1991;38(5):417-20.

116. Gurwitz JH, Field TS, Avorn J, et al. Incidence and preventability of adverse drug events in nursing homes. *The American Journal of Medicine.* 2000;109(2):87-94.

117. Howard R, Avery A, Slavenburg S, et al. Which drugs cause preventable admissions to hospital? A systematic review. *British Journal of Clinical Pharmacology.* 2007;63(2):136-47.

118. Bigby J, Dunn J, Goldman L, et al. Assessing the preventability of emergency hospital admissions. A method for evaluating the quality of medical care in a primary care facility. *The American Journal of Medicine.* 1987;83(6):1031-6.

119. Ruths S, Straand J, Nygaard HA. Multidisciplinary medication review in nursing home residents: what are the most significant drug-related problems? The Bergen District Nursing Home (BEDNURS) study. *Quality & Safety in Health Care*. 2003;12(3):176-80.

120. Nguyen JK, Fouts MM, Kotabe SE, Lo E. Polypharmacy as a risk factor for adverse drug reactions in geriatric nursing home residents. *American Journal of Geriatrics Pharmacotherapy*. 2006;4(1):36-41. doi:10.1016/j.amjopharm.2006.03.002.

121. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. Ann Intern Med. 2003;138(3):161-7.

122. Hardmeier B, Braunschweig S, Cavallaro M, et al. Adverse drug events caused by medication errors in medical inpatients. *Swiss Medical Weekly*. 2004;134(45-46):664-70. doi:2004/45/smw-10801.

123. National board of health, 2009 annual report: The Danish patient safety database(DPSD),*Copenhagen,* February 2010. Viahttps://laegemiddelstyrelsen.dk/en/publications/2011/publication-on-medicines-most-frequently-involved-in-serious-adverse-drug-events/~/media/D351DCAA2DB4463498724643F4E876C6.ashx.

124. Holm E, Brorson SW, Kruse JS et al. Medicines most frequently involved in serious adverse drug events. *Journal of the Danish Medical Association.* 2004;45.

125. Howard RL, Avery AJ, Howard PD, Partridge M. Investigation into the reasons for preventable drug related admissions to a medical admissions unit: Observational study. *Quality & Safety In Health Care.* 2003;12(4):280-5.

126. Hallas J, Gram LF, Grodum E, et al. Drug related admissions to medical wards: A population based survey. *British Journal of Clinical Pharmacology.* 1992;33(1):61-8.

127. Gurwitz JH, Field TS, Judge J, et al. The incidence of adverse drug events in two large academic long-term care facilities. *The American Journal of Medicine.* 2005;118(3):251-8. doi:10.1016/j.amjmed.2004.09.018.

128. Nebeker JR, Hoffman JM, Weir CR, Bennett CL, Hurdle JF. High rates of adverse drug events in a highly computerized hospital. *Archives of Internal Medicine.* 2005;165(10):1111-6. doi:10.1001/archinte.165.10.1111.

129. Chrischilles EA, Segar ET, Wallace RB. Self-reported adverse drug reactions and related resource use. A study of community-dwelling persons 65 years of age and older. *Annals of Internal Medicine.* 1992;117(8):634-40.

130. Dartnell JG, Anderson RP, Chohan V, et al. Hospitalisation for adverse events related to drug therapy: incidence, avoidability and costs. *The Medical Journal of Australia*. 1996;164(11):659-62.

131. Parameswaran Nair N, Chalmers L, Bereznicki BJ, et al. Adverse drug reaction-related hospitalizations in elderly australians: A Prospective cross-sectional study in two Tasmanian Hospitals. *Drug Safety.* 2017;40(7):597-606. doi:10.1007/s40264-017-0528-z

132. Holt MP, Ju C. Mechanisms of drug-induced liver injury. *The AAPS Journal: An Official Journal of the American Association of Pharmaceutical Scientists.* 2006;8(1):E48-54. doi:10.1208/aapsj080106.

133. Reuben A, Koch DG, Lee WM. Drug-induced acute liver failure: Results of a US multicenter, prospective study. *Hepatology.* 2010;52(6):2065-76. doi:10.1002/hep.23937.

134. Lee WM. Drug-induced acute liver failure. *Clinical Liver Disease.* 2013;17(4):575-86, viii. doi:10.1016/j.cld.2013.07.001.

135. Wilke RA, Lin DW, Roden DM, et al. Identifying genetic risk factors for serious adverse drug reactions: Current progress and challenges. *Nature Reviews. Drug Discovery.* 2007;6(11):904-16. doi:10.1038/nrd2423.

136. Haque T, Sasatomi E, Hayashi PH. Drug-induced liver injury: Pattern recognition and future directions. *Gut and Liver.* 2016;10(1):27-36. doi:10.5009/gnl15114.

137. Carey EJ, Vargas HE, Douglas DD, et al. Inpatient admissions for drug-induced liver injury: results from a single center. *Digestive Diseases and Sciences.* 2008;53(7):1977-82. doi:10.1007/s10620-008-0250-x.

138. Ghabril M, Chalasani N, Bjornsson E. Drug-induced liver injury: A clinical update. *Current Opinion in Gastroenterology.* 2010;26(3):222-6. doi:10.1097/MOG.0b013e3283383c7c.

139. Björnsson ES. Hepatotoxicity by drugs: The most common implicated agents. *International Journal of Molecular Sciences*. 2016;17(2). doi:10.3390/ijms17020224.

140. Hou FQ, Zeng Z, Wang GQ. Hospital admissions for drug-induced liver injury: Clinical features, therapy, and outcomes. *Cell Biochemistry and Biophysics.* 2012;64(2):77-83. doi:10.1007/s12013-012-9373-y.

141. Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *Jounal of Hepatology.* 1990;11(2):272-6.

142. Bussieres JF, Habra M. Application of International Consensus Meeting Criteria for classifying drug-induced liver disorders. *Annals of Pharmacotherapy.* 1995;29(9):875-8. doi:10.1177/106002809502900910.

143. Mueller BA. Acute renal failure. In: Pharmacotherapy. 6th ed. New York, NY McGraw-Hill; 2005;781-90.

144. Hannah RH, Brundige ML, Lindsay L. Drug-induced acute renal failure. US Pharmacy. *Nephrology*. 2007;32(3):45-50.

145. Schetz M, Dasta J, Goldstein S, Golper T. Drug-induced acute kidney injury. *Current Opinion in Critical Care*. 2005;11(6):555-65.

146. Ghane Shahrbaf F, Assadi F. Drug-induced renal disorders. *Journal of Renal Injury Prevention*. 2015;4(3):57-60. doi:10.12861/jrip.2015.12.

147. Angamo MT, Curtain CM, Chalmers L, Yilma D, Bereznicki L. Predictors of adverse drug reaction-related hospitalisation in Southwest Ethiopia: A prospective cross-sectional study. *PLoS One.* 2017;12(10):e0186631. doi:10.1371/journal.pone.0186631

148. Koselj M, Kveder R, Bren AF, Rott T. Acute renal failure in patients with drug-induced acute interstitial nephritis. *Renal Failure.* 1993;15(1):69-72.

149. Pannu N, Nadim MK. An overview of drug-induced acute kidney injury. *Critical Care Medicine.* 2008;36(4 Suppl):S216-23. doi:10.1097/CCM.0b013e318168e375.

150. Agostini JV, Han L, Tinetti ME. The relationship between number of medications and weight loss or impaired balance in older adults. *Journal of the American Geriatrics Society.* 2004;52(10):1719-23. doi:10.1111/j.1532-5415.2004.52467.x.

151. Camargo AL, Cardoso Ferreira MB, Heineck I. Adverse drug reactions: A cohort study in internal medicine units at a university hospital. *European Journal of Clinical Pharmacology*. 2006;62:143-9.

152. Dormann H, Neubert A, Criegee-Rieck M, et al. Readmissions and adverse drug reactions in internal medicine: the economic impact. *Journal of Internal Medicine.* 2004;255(6):653-63.

153. Hakkarainen KM, Andersson Sundell K, Petzold M, Hagg S. Methods for assessing the preventability of adverse drug events: A systematic review. *Drug Safety.* 2012;35(2):105-26. doi:10.2165/11596570-000000000-00000.

154. Sikdar KC, Alaghehbandan R, MacDonald D, et al. Adverse drug events in adult patients leading to emergency department visits. *Annals of Pharmacotherapy.* 2010;44(4):641-9. doi:10.1345/aph.1M416.

155. Trifirò G, Calogero G, Ippolito FM, et al. Adverse drug events in emergency department population: a prospective Italian study. *Pharmacoepidemiology and Drug Safety.* 2005;14(5):333-40.

156. Tumwikirize WA, Ogwal-Okeng JW, Vernby A, et.al. Adverse drug reactions in patients admitted on internal medicine wards in a district and regional hospital in Uganda. *African Health Sciences.* 2011;11(1):72-8.

157. Aljadhey H, Mahmoud MA, Mayet A, et al. Incidence of adverse drug events in an academic hospital: A prospective cohort study. *International Journal for Quality in Health Care : Journal of the International Society for Quality in Health Care / ISQUA.* 2013;25(6):648-55. doi:10.1093/intqhc/mzt075.

158. Baena MI, Fajardo PC, Pintor-Marmol A, et al. Negative clinical outcomes of medication resulting in emergency department visits. *European Journal of Clinical Pharmacology.* 2014;70(1):79-87. doi:10.1007/s00228-013-1562-0.

159. Boockvar K, Fishman E, Kyriacou CK, Monias A, Gavi S, Cortes T. Adverse events due to discontinuations in drug use and dose changes in patients transferred between acute and long-term care facilities. *Archives of Internal Medicine.* 2004;164(5):545-50. doi:10.1001/archinte.164.5.545.

160. Chan M, Nicklason F, Vial JH. Adverse drug events as a cause of hospital admission in the elderly. *Internal Medicine Journal.* 2001;31(4):199-205.

161. Devi P, Kamath DY, Anthony N, Santosh S, Dias B. Patterns, predictors and preventability of adverse drug reactions in the coronary care unit of a tertiary care hospital. *European Journal of Clinical Pharmacology.* 2012;68(4):427-33. doi:10.1007/s00228-011-1138-9.

162. Hassen AA, Belachew T, Yami A, Ayen WY. Anti-Tuberculosis Drug induced hepatotoxicity among TB/HIV co-infected patients at Jimma University Hospital, Ethiopia: Nested case-control study. *PLoS One.* 2013;8(5):e64622. doi:doi:10.1371/journal.pone.0064622.

163. Kongkaew C, Hann M, Mandal J, et al. Risk factors for hospital admissions associated with adverse drug events. *Pharmacotherapy.* 2013;33(8):827-37. doi:10.1002/phar.1287.

164. Roulet L, Asseray N, Dary M, Chiffoleau A, Potel G, Ballereau F. Implementing a clinical pharmacy survey of adverse drug events in a French emergency department.

International Journal of Clinical Pharmacy. 2012;34(6):902-10. doi:10.1007/s11096-012-9691-6.

165. Sharifzadeh M, Rasoulinejad M, Valipour F, Nouraie M, Vaziri S. Evaluation of patient-related factors associated with causality, preventability, predictability and severity of hepatotoxicity during antituberclosis treatment. *Pharmacological Research.* 2005;51(4):353-8.

166. Mjorndal T, Boman MD, Hagg S, et al. Adverse drug reactions as a cause for admissions to a department of internal medicine. *Pharmacoepidemiology and Drug Safety*. 2002;11(1):65-72. doi:10.1002/pds.667.

167. Hellden A, Bergman U, von Euler M, Hentschke M, Odar-Cederlof I, Ohlen G. Adverse drug reactions and impaired renal function in elderly patients admitted to the emergency department: a retrospective study. *Drugs & Aging.* 2009;26(7):595-606. doi:10.2165/11315790-000000000-00000.

168. Alomar MJ. Factors affecting the development of adverse drug reactions (Review article). *Saudi Pharmaceutical Journal : SPJ : The Official Publication of the Saudi Pharmaceutical Society*. 2014;22(2):83-94. doi:10.1016/j.jsps.2013.02.003.

169. Zopf Y, Rabe C, Neubert A, et al. Women encounter ADRs more often than do men. *European Journal of Clinical Pharmacology.* 2008;64(10):999-1004. doi:10.1007/s00228-008-0494-6.

170. Hug BL, Witkowski DJ, Sox CM, et al. Adverse drug event rates in six community hospitals and the potential impact of computerized physician order entry for prevention. *Journal of General Internal Medicine.* 2010;25(1):31-8. doi:10.1007/s11606-009-1141-3.

171. Rodenburg EM, Stricker BH, Visser LE. Sex differences in cardiovascular drug-induced adverse reactions causing hospital admissions. *British Journal of Clinical Pharmacology.* 2012;74(6):1045-52. doi:10.1111/j.1365-2125.2012.04310.x.

172. Waxman DJ, Holloway MG. Sex differences in the expression of hepatic drug metabolizing enzymes. *Molecular Pharmacology*. 2009;76(2):215-28. doi:10.1124/mol.109.056705.

173. El-Eraky H, Thomas SH. Effects of sex on the pharmacokinetic and pharmacodynamic properties of quinidine. *British Journal of Clinical Pharmacology.* 2003;56(2):198-204.

174. Mitchell SC, Smith RL, Waring RH. The menstrual cycle and drug metabolism. *Current Drug Metabolism.* 2009;10(5):499-507.

175. Ensom MH. Gender-based differences and menstrual cycle-related changes in specific diseases: Implications for pharmacotherapy. *Pharmacotherapy.* 2000;20(5):523-39.

176. Zhang M, Holman CDJ, Price SD, Sanfilippo FM, Preen DB, Bulsara. Comorbidity and repeat admission to hospital for adverse drug reactions in older adults: Retrospective cohort study. *British Medical Journal.* 2009;338. doi:10.1136/bmj.a2752.

177. Franz CC, Egger S, Born C, Ratz Bravo AE, Krahenbuhl S. Potential drug-drug interactions and adverse drug reactions in patients with liver cirrhosis. *European Journal of Clinical Pharmacology.* 2012;68(2):179-88. doi:10.1007/s00228-011-1105-5.

178. Zuckerman MJ, Menzies IS, Ho H, et al. Assessment of intestinal permeability and absorption in cirrhotic patients with ascites using combined sugar probes. *Digestive Diseases and Sciences.* 2004;49(4):621-6.

179. Blaschke TF, Rubin PC. Hepatic first-pass metabolism in liver disease. *Clinical Pharmacokinetics.* 1979;4(6):423-32.

180. Delco F, Tchambaz L, Schlienger R, Drewe J, Krahenbuhl S. Dose adjustment in patients with liver disease. *Drug Safety*. 2005;28(6):529-45.

181. Gonzalez M, Goracci L, Cruciani G, Poggesi I. Some considerations on the predictions of pharmacokinetic alterations in subjects with liver disease. *Expert Opinion on Drug Metabolism & Toxicology.* 2014;10(10):1397-408. doi:10.1517/17425255.2014.952628.

182. Franz CC, Hildbrand C, Born C, Egger S, Ratz Bravo AE, Krahenbuhl S. Dose adjustment in patients with liver cirrhosis: impact on adverse drug reactions and hospitalizations. *European Journal of Clinical Pharmacology.* 2013;69 (8):1565-73. doi:10.1007/s00228-013-1502-z.

183. Olyaei AJ, Steffl JL. A quantitative approach to drug dosing in chronic kidney disease. *Blood Purification.* 2011;31(1-3):138-45. doi:10.1159/000321857.

184. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *British Journal of Clinical Pharmacology.* 2004;57(1):6-14.

185. Fink JC, Brown J, Hsu VD, Seliger SL, Walker L, Zhan M. CKD as an underrecognized threat to patient safety. *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation.* 2009;53(4):681-8. doi:10.1053/j.ajkd.2008.12.016.

186. Caamano F, Pedone C, Zuccala G, Carbonin P. Socio-demographic factors related to the prevalence of adverse drug reaction at hospital admission in an elderly population. *Archives of Gerontology and Geriatrics.* 2005;40(1):45-52. doi:10.1016/j.archger.2004.05.005.

187. Hoigne R, Sollberger J, Zoppi M, et al. Significance of age, sex, kidney function, atopy and number of prescriptions for the occurrence of adverse drug reactions, studied by multivariate statistical methods. Results from the Comprehensive Hospital Drug Monitoring Berne (CHDMB). *Schweizerische medizinische Wochenschrift.* 1984;114(49):1854-7.

188. Bruce RD, Altice FL, Friedland GH. Pharmacokinetic drug interactions between drugs of abuse and antiretroviral medications: Implications and management for clinical practice. *Expert Review of Clinical Pharmacology.* 2008;1(1):115-27. doi:10.1586/17512433.1.1.115.

189. Krupski A, Campbell K, Joesch JM, Lucenko BA, Roy-Byrne P. Impact of access to recovery services on alcohol/drug treatment outcomes. *Journal of Substance Abuse Treatment.* 2009;37(4):435-42. doi:10.1016/j.jsat.2009.05.007.

190. Kim BH, Yi S, Kim J, et al. Influence of alcohol on the hemodynamic effects and pharmacokinetic properties of mirodenafil: A single-dose, randomized-sequence, open-label, crossover study in healthy male volunteers in Korea. *Clinical Therapeutics.* 2009;31(6):1234-43. doi:10.1016/j.clinthera.2009.06.008.

191. Onder G, Landi F, Della Vedova C, et al. Moderate alcohol consumption and adverse drug reactions among older adults. *Pharmacoepidemiology and Drug Safety*. 2002;11(5):385-92.

192. Przybylski G, Dabrowska A, Trzcinska H. Alcoholism and other socio-demographic risk factors for adverse TB-drug reactions and unsuccessful tuberculosis treatment - data from ten years' observation at the Regional Centre of Pulmonology, Bydgoszcz, Poland. *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research.* 2014;20:444-53. doi:10.12659/msm.890012.

193. Gupta KB, Gupta R, Atreja A, Verma M, Vishvkarma S. Tuberculosis and Nutrition. *Lung India : Official Organ of Indian Chest Society*. 2009;26(1):9-16. doi:10.4103/0970-2113.45198.

194. Tverdal A. Body mass index and incidence of tuberculosis. *European Journal of Respiratory Diseases.* 1986;69(5):355-62.

195. Sudre P, ten Dam G, Kochi A. Tuberculosis: A global overview of the situation today. *Bulletin of the World Health Organisation.* 1992;70(2):149-59.

196. Krishnaswamy K. Drug metabolism and pharmacokinetics in malutrition. *Clinical Pharmacokinetics.* 1978;3(3):216-40.

197. Pamela M. Undernutrition in hospital: Causes and consequences. *Hospial Pharmacist.* 2006;13:353-8.

198. Purnak T, Yilmaz Y. Liver disease and malnutrition. Best practice & research. *Clinical Gastroenterology.* 2013;27(4):619-29. doi:10.1016/j.bpg.2013.06.018.

199. Dimie O, Reginald OO, Haruna MM, et al. Morbidity andMortality Patterns of Hospitalised Adult HIV/AIDS Patients in the Era of Highly Active Antiretroviral Therapy: A 4-year Retrospective Review from Zaria, Northern Nigeria. *AIDS Research and Treatment.* 2012;2012:1-11. doi:10.1155/2012/940580.

200. Henry NL, Marie-Solange D, Simeon-Pierre C, et al. Adverse drug reactions of Highly Active Antiretroviral Therapy (HAART) in HIV infected patients at the General Hospital, Douala, Cameroon: a cross sectional study. *The Pan African Medical Journal.* 2012;12(87):1-7.

201. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hospital Pharmacy.* 1992;27(6):538.

202. Hallas J, Harvald B, Gram LF, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *Journal of Internal Medicine.* 1990;228(2):83-90.

203. Letrilliart L, Hanslik T, Biour M, Fagot JP, Guiguet M, Flahault A. Postdischarge adverse drug reactions in primary care originating from hospital care in France: A nationwide prospective study. *Drug Safety.* 2001;24(10):781-92.

204. Thomas EJ, Lipsitz SR, Studdert DM, et al. The reliability of medical record review for estimating adverse event rates. Annals of Internal Medicine. 2002;136(11):812-6.

205. Snyder RA, Abarca J, Meza JL, et.al. Reliability evaluation of the adapted national coordinating council medication error reporting and prevention (NCC MERP) index. *Pharmacoepidemiology and Drug Safety.* 2007;16(9):1006-13.

206. Farcas A, Sinpetrean A, Mogosan C, et al. Adverse drug reactions detected by stimulated spontaneous reporting in an internal medicine department in Romania. *European Journal of Internal Medicine.* 2010;21(5):453-7. doi:10.1016/j.ejim.2010.05.014.

207. Rommers MK, Teepe-Twiss IM, Guchelaar HJ. Preventing adverse drug events in hospital practice: an overview. *Pharmacoepidemiology and Drug Safety.* 2007;16(10):1129-35. doi:10.1002/pds.1440.

208. Onder G, Petrovic M, Tangiisuran B, et al. Development and validation of a score to assess risk of adverse drug reactions among in-hospital patients 65 years or older: The GerontoNet ADR risk score. *Archives of Internal Medicine.* 2010;170(13):1142-8. doi:10.1001/archinternmed.2010.153.

209. Tangiisuran B, Scutt G, Stevenson J, et al. Development and validation of a risk model for predicting adverse drug reactions in older people during hospital stay: Brighton Adverse Drug Reactions Risk (BADRI) Model. *PLoS One.* 2014;9(10):e111254. doi:10.1371/journal.pone.0111254.

210. Elnicki RA, Schmitt JP. Contribution of patient and hospital characteristics to adverse patient incidents. *Health Services Research.* 1980;15(4):397-414.

211. Bates DW, Miller EB, Cullen DJ, et al. Patient risk factors for adverse drug events in hospitalized patients. ADE Prevention Study Group. *Archives of Internal Medicine.* 1999;159(21):2553-60.

212. Johnston PE, France DJ, Byrne DW, et al. Assessment of adverse drug events among patients in a tertiary care medical center. *American Journal of Health-System Pharmacy : AJHP : Official Journal of the American Society of Health-System Pharmacists.* 2006;63(22):2218-27. doi:10.2146/ajhp050405.

213. Parameswaran Nair N, Chalmers L, Connolly M, et al. Prediction of hospitalization due to adverse drug reactions in elderly community-dwelling patients (The PADR-EC Score). *PLoS One.* 2016;11(10):e0165757. doi:10.1371/journal.pone.0165757.

214. USAID/SPS (Strengthening Pharmaceutical System) program. Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance. 2011. Via https://africapv2012.files.wordpress.com/2012/05/day-1_2_findings-from-the-ssa-study_nwokike.pdf.

215. Smith CC, Bennett PM, Pearce HM, et al. Adverse drug reactions in a hospital general medical unit meriting notification to the Committee on Safety of Medicines. *British Journal of Clinical Pharmacology.* 1996;42(4):423-9.

216. Cox AR, Anton C, Goh CH, Easter M, Langford NJ, Ferner RE. Adverse drug reactions in patients admitted to hospital identified by discharge ICD-10 codes and by spontaneous reports. *British Journal of Clinical Pharmacology*. 2001;52(3):337-9.

217. Molokhia M, Tanna S, Bell D. Improving reporting of adverse drug reactions: Systematic review. *Clinical Epidemiology.* 2009;1:75-92.

218. Baniasadi S, Habibi M, Haghgoo R, et al. Increasing the number of adverse drug reactions reporting: The role of clinical pharmacy residents. *Iranian Journal of Pharmaceutical Research : IJPR.* 2014;13(1):291-7.

219. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Archives of Internal Medicine*. 2005;165(10):1095-106. doi:10.1001/archinte.165.10.1095.

220. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *Journal of Amerivcan Medical Association.* 2003;289(13):1652-8. doi:10.1001/jama.289.13.1652.

221. Chumney EC, Robinson LC. The effects of pharmacist interventions on patients with polypharmacy. *Pharmacy Practice (Granada).* 2006;4(3):103-9.

222. Nuckols TK, Smith-Spangler C, Morton SC, et al. The effectiveness of computerized order entry at reducing preventable adverse drug events and medication errors in hospital settings: A systematic review and meta-analysis. *Systematic Reviews.* 2014;3:56. doi:10.1186/2046-4053-3-56.

223. Steinman MA, Handler SM, Gurwitz JH, Schiff GD, Covinsky KE. Beyond the prescription: medication monitoring and adverse drug events in older adults. *Journal of the American Geriatrics Society.* 2011;59(8):1513-20. doi:10.1111/j.1532-5415.2011.03500.x.

224. Kang JS, Lee MH. Overview of therapeutic drug monitoring. *The Korean Journal of Internal Medicine.* 2009;24(1):1-10. doi:10.3904/kjim.2009.24.1.1.

225. Monitoring drug therapy: Three steps for pharmacists. *American Pharmacists Association.* Available from. Via. https://www.pharmacytoday.org/article/S1042-0991(15)31950-2/fulltext.

226. Margaret Duguid. The importance of medication reconciliation for patients and practitioners. *Australian Prescriber.* 2012;35(1):15-9. doi:10.18773/austprescr.2012.007

227. Rozich JD, Howard RJ, Justeson JM, Macken PD, Lindsay ME, Resar RK. Standardisation as a mechanism to improve safety in health care. *Joint Commission Journal on Quality and Safety.* 2004;30(1):5-14.

228. Gleason KM, Groszek JM, Sullivan C, Rooney D, Barnard C, Noskin GA. Reconciliation of discrepancies in medication histories and admission orders of newly

hospitalized patients. *American Journal of Health-System Pharmacy : AJHP : Official Journal of the American Society of Health-System Pharmacists.* 2004;61(16):1689-95.

229. Mekonnen AB, McLachlan AJ, Brien JA. Pharmacy-led medication reconciliation programmes at hospital transitions: A systematic review and meta-analysis. *Journal of Clinical Pharmacy and Therapeutics.* 2016;41(2):128-44. doi:10.1111/jcpt.12364.

230. Gray SL, Hart LA, Perera S, Semla TP, Schmader KE, Hanlon JT. Meta-analysis of Interventions to Reduce Adverse Drug Reactions in Older Adults. *Journal of the American Geriatrics Society.* 2017. doi:10.1111/jgs.15195.

231. Thomas R, Huntley AL, Mann M, et al. Pharmacist-led interventions to reduce unplanned admissions for older people: a systematic review and meta-analysis of randomised controlled trials. Age and Ageing. 2014;43(2):174-87. doi:10.1093/ageing/aft169.

232. Chen TF. Pharmacist-Led Home Medicines Review and Residential Medication Management Review: *The Australian Model. Drugs & Aging.* 2016;33(3):199-204. doi:10.1007/s40266-016-0357-2

233. Furniss L, Burns A, Craig SK, Scobie S, Cooke J, Faragher B. Effects of a pharmacist's medication review in nursing homes. Randomised controlled trial. *The British Journal of Psychiatry : The Journal of Mental Science.* 2000;176:563-7.

234. Nishtala PS, Hilmer SN, McLachlan AJ, Hannan PJ, Chen TF. Impact of residential medication management reviews on drug burden index in aged-care homes: A retrospective analysis. *Drugs & Aging.* 2009;26(8):677-86. doi:10.2165/11316440-000000000-00000

235. Christensen D, Trygstad T, Sullivan R, Garmise J, Wegner SE. A pharmacy management intervention for optimizing drug therapy for nursing home patients. *American Journal of Geriatric Pharmacotherapy.* 2004;2(4):248-56.

236. Etzel JV, Brocavich JM, Rousseau M. Impact of the development of a multidisciplinary adverse drug reaction committee. *Hospital Pharmacy.* 1995;30(12):1083-7.

237. Pretorius RW, Gataric G, Swedlund SK, Miller JR. Reducing the risk of adverse drug events in older adults. American family physician. 2013;87(5):331-6.

238. O'Connor MN, O'Sullivan D, Gallagher PF, Eustace J, Byrne S, O'Mahony D. Prevention of hospital-acquired adverse drug reactions in older people using screening tool of older persons' prescriptions and screening tool to alert to right treatment Criteria: A cluster randomized controlled trial. *Journal of the American Geriatrics Society.* 2016;64(8):1558-66. doi:10.1111/jgs.14312

239. American Geriatrics Society 2015 Updated Beers criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society.* 2015;63(11):2227-46. doi:10.1111/jgs.13702.

240. American Geriatrics Society updated Beers criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society.* 2012;60(4):616-31. doi:10.1111/j.1532-5415.2012.03923.x.

241. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. *Archives of Internal Medicine.* 2011;171(11):1013-9. doi:10.1001/archinternmed.2011.215.

242. Vishwas HN, Harugeri A, Parthasarathi G, Ramesh M. Potentially inappropriate medication use in Indian elderly: comparison of Beers' criteria and Screening Tool of Older Persons' potentially inappropriate Prescriptions. *Geriatrics & Gerontology International.* 2012;12(3):506-14. doi:10.1111/j.1447-0594.2011.00806.x.

243. Hanlon JT, Schmader KE. What types of inappropriate prescribing predict adverse drug reactions in older adults? *Annals of Pharmacotherapy.* 2010;44(6):1110-1. doi:10.1345/aph.1P182.

244. Hanlon JT, Schmader KE. The medication appropriateness index at 20: Where it started, where it has been, and where it may be going. *Drugs & Aging.* 2013;30(11):893-900. doi:10.1007/s40266-013-0118-4.

245. Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. *Journal of Clinical Epidemiology.* 1992;45(10):1045-51.

246. Khong TK, Singer DR. Adverse drug reactions: Current issues and strategies for prevention and management. *Expert Opinion on Pharmacotherapy.* 2002;3(9):1289-300. doi:10.1517/14656566.3.9.1289.

247. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *Journal of Amrican Medical Association.* 1998;280(15):1311-6.

248. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: A systematic review. *Archives of Internal Medicine.* 2003;163(12):1409-16. doi:10.1001/archinte.163.12.1409.

249. The medical reference app. Via http://www.epocrates.com/.

250. McDowell SE, Coleman JJ, Ferner R. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. *British Medical Journal* 2006;332(7551):1177-81.

251. Aziz Z, Siang TC, Badarudin NS. Reporting of adverse drug reactions: Predictors of under-reporting in Malaysia. *Pharmacoepidemiology and Drug Safety.* 2007;16(2):223-8. doi:10.1002/pds.1313.

252. Rehan HS, Vasudev K, Tripathi CD. Adverse drug reaction monitoring: Knowledge, attitude and practices of medical students and prescribers. *The National Medical Journal of India.* 2002;15(1):24-6.

253. Federal Democratic Republic of Ethiopia Ministry of Health. Health Sector Development Program IV 2010/11 – 2014/15 2010. via http://www.nationalplanningcycles.org/sites/default/files/country_docs/Ethiopia/ethiopia_hsdp_iv_final_draft_2010_-2015.pdf. Accessed on Oct 2018.

254. Banteyerga H. Ethiopia's health extension program: Improving health through community involvement. *MEDICC review.* 2011;13(3):46-9.

255. Ministry of Health. Quarterly Health Bulletin. Policy and Practice: Information for Action. Addis Ababa, Ethiopia: *Federal Democratic Republic of Ethiopia Ministry of Health.* 2013.

256. Ethiopia's Health Extension Program. Via http://www2.pathfinder.org/site/DocServer/CBRHAs__HEWs_REVISED_REPRINT__2_.pdf?docID=11303. Accessed on Oct 2018. 2008.

257. Federal Democratic Republic of Ethiopia Ministry of Health. Guideline for implementation of a patient referral system. 2010.

258. Jimma University Specialised Hospital. https://www.ju.edu.et/jimma-university-specialized-hospital-jush. Accessed on 28 December 2016 at 12:39PM.

259. Ethiopian Food Medicine, Health Adminstration and Control authority (FMHACA). Guideline for adverse drug events monitoring (Pharmacovigilance). *FMHACA* . 2014.

260. Ermias A, Gurmesa G, Mesfin M, Mengistu A. Adverse Drug Reaction Monitoring in Ethiopia: Analysis of case reports, 2002-2007. *Ethiopian Journal of Health Development.* 2011;25(2):168-73.

261. Members of the WHO Programme for International Drug Monitoring. Via https://www.who-umc.org/global-pharmacovigilance/members/who-programme-members/. Accessed on Oct 2018. .

262. Gurmesa LT, Dedefo MG. Factors Affecting adverse drug reaction reporting of healthcare professionals and their knowledge, attitude, and practice towards adr reporting in Nekemte Town, West Ethiopia. *Biomed Research International.* 2016;2016:5728462. doi:10.1155/2016/5728462

263. Seid MA, Kasahun AE, Mante BM, Gebremariam SN. Healthcare professionals' knowledge, attitude and practice towards adverse drug reaction (ADR) reporting at the health center level in Ethiopia. *International Journal of Clinical Pharmacy*. 2018;40(4):895-902. doi:10.1007/s11096-018-0682-0

264. Shanko H, Abdela J. Knowledge, attitudes, and practices of health care professionals toward adverse drug reaction reporting in Hiwot Fana Specialized University Hospital, Harar,

Eastern Ethiopia: A Cross-sectional study. *Hospital Pharmacy.* 2018;53(3):177-87. doi:10.1177/0018578717737430

265. Doherty J M. Algorithms for assessing the probability of an adverse drug reaction. 2009.

266. Melmon KL. Preventable drug reactions causes and cures. *The New England Journal of Medicine.* 1971;284(24):1361-8. doi:10.1056/nejm197106172842408

267. Wester K, Jonsson AK, Spigset O, Druid H, Hagg S. Incidence of fatal adverse drug reactions: a population based study. *British Journal of Clinical Pharmacology.* 2008;65(4):573-9. doi:10.1111/j.1365-2125.2007.03064.x.

268. United Nations Acquired Immunodeficiency Syndrome (UNAIDS) global update 2016. Via: http://www.who.int/ hiv/mediacentre/news/global-aids-update-2016-news/en/. Accessed on 24 June 2017.

269. Isah AO, Pal SN, Olsson S, Dodoo A, Bencheikh RS. Specific features of medicines safety and pharmacovigilance in Africa. *Therapeutic Advances in Drug Safety.* 2012;3(1):25-34. doi:10.1177/2042098611425695.

270. Subbaraman R, Chaguturu SK, Mayer KH, Flanigan TP, Kumarasamy N. Adverse effects of highly active antiretroviral therapy in developing countries. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America.* 2007;45(8):1093-101. doi:10.1086/521150.

271. Yimer G, Ueda N, Habtewold A, et al. Pharmacogenetic & pharmacokinetic biomarker for efavirenz based ARV and rifampicin based anti-TB drug induced liver injury

in TB-HIV infected patients. *PLoS One.* 2011;6(12):e27810. doi:10.1371/journal.pone.0027810.

272. Aminkeng F, Ross CJ, Rassekh SR, et al. Higher frequency of genetic variants conferring increased risk for ADRs for commonly used drugs treating cancer, AIDS and tuberculosis in persons of African descent. *The Pharmacogenomics Journal.* 2014;14(2):160-70. doi:10.1038/tpj.2013.13.

273. Van Olmen J, Schellevis F, Van Damme W, Kegels G, Rasschaert F. Management of chronic diseases in sub-Saharan Africa: Cross-fertilisation between HIV/AIDS and diabetes care. *Journal of Tropical Medicine.* 2012;2012:349312. doi:10.1155/2012/349312.

274. Misganaw A, Mariam DH, Ali A, Araya T. Epidemiology of major non-communicable diseases in Ethiopia: a systematic review. *Journal of Health, Population, and Nutrition.* 2014;32(1):1-13.

275. Hunchak C, Teklu S, Meshkat N, Meaney C, Puchalski Ritchie L. Patterns and predictors of early mortality among emergency department patients in Addis Ababa, Ethiopia. *BMC Research Notes.* 2015;8:605. doi:10.1186/s13104-015-1592-z.

276. Misganaw A, Mariam DH, Araya T, Ayele K. Patterns of mortality in public and private hospitals of Addis Ababa, Ethiopia. *BMC Public Health.* 2012;12:1007. doi:10.1186/1471-2458-12-1007.

277. Ethiopian Federal Ministry of Health HIV/AIDS Prevention and Control Office Country progress report in HIV/AIDS response. *Addis Ababa: Ethiopian Federal Ministry of Health HIV/AIDS Prevention and Control Office*, 2014.

278. Netsanet WW, Gandham NVR. Health extension program in Ethiopia. Universal health coverage studies series (UNICO) No.10. The World Bank, Washington DC; 2013. Via http://documents.worldbank.org/curated/en/356621468032070256/Ethiopia-The-health-extension-program-in-Ethiopia.

279. Gedle D, Gelaw B, Muluye D, Mesele M. Prevalence of malnutrition and its associated factors among adult people living with HIV/AIDS receiving anti-retroviral therapy at Butajira Hospital, southern Ethiopia. *BMC Nutrition.* 2015;1(1):5. doi:10.1186/2055-0928-1-5.

280. Dargie B, Tesfaye G, Worku A. Prevalence and associated factors of undernutrition among adult tuberculosis patients in some selected public health facilities of Addis Ababa, Ethiopia: a cross-sectional study. *BMC Nutrition.* 2016;2(1):7. doi:10.1186/s40795-016-0046-x.

281. European Commission. Pharmacovigilance impact assessment.2008.via http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/pharmacovigilance-ia-vol1_en.pdf.

282 Alhawassi TM, Krass I, Bajorek BV, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. *Clinical Interventions in Aging.* 2014;9:2079-86. doi:10.2147/cia.s71178.

283. World Health Organisation. Safety of Medicine: A guide to detecting and reporting adverse drug reaction.*WHO. Geneva.* 2002.

284. Al Hamid A, Ghaleb M, Aljadhey H, Aslanpour Z. A systematic review of hospitalization resulting from medicine-related problems in adult patients. *British Journal of Clinical Pharmacology.* 2014;78(2):202-17. doi:10.1111/bcp.12293.

285. Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): A meta-analysis of observational studies. *Pharmacy World Sciences.* 2002;24(2):46-54.

286. Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: A systematic review of prospective observational studies. *Annals of Pharmacotherapy.* 2008;42(7):1017-25.

287. CIA. Country comparison: Life expectancy at birth. 2015.Via https://www.cia.gov/library/publications/the-world-factbook/rankorder/2102rank.html. Accessed on June 9, 2016 at 5:50PM.

288. WHO. Counterfeit Medicines: An update on estimates.2006. http://www.who.int/medicines/services/counterfeit/impact/The New Estimates Counterfeit.pdf. Accessed on June,2016.

289. World Bank. Comparing levels of development.2000. Via http://www.worldbank.org/depweb/beyond/beyondco/beg_02.pdf. Accessed on Decemeber 22, 2015 at 3:00PM.

290. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *New England Journal of Medicine.* 2011;365(21):2002-12.

291. Chen YC, Fan JS, Chen MH, et al. Risk factors associated with adverse drug events among older adults in emergency department. *European Journal of Internal Medicine.* 2014;25(1):49-55. doi:10.1016/j.ejim.2013.10.006.

292. Lagnaoui R, Moore N, Fach J, Longy-Boursier M, Begaud B. Adverse drug reactions in a department of systemic diseases-oriented internal medicine: Prevalence, incidence, direct costs and avoidability. *European Journal of Clinical Pharmacology*. 2000;56(2):181-6.

293. Matanovic SM, Vlahovic-Palcevski V. Potentially inappropriate prescribing to the elderly: comparison of new protocol to Beers criteria with relation to hospitalizations for ADRs. *European Journal of Clinical Pharmacology*. 2014;70(4):483-90. doi:10.1007/s00228-014-1648-3.

294. Walsh D, Lavan A, Cushen AM, Williams D. Adverse drug reactions as a cause of admission to a Dublin-based university teaching hospital. *Irish Journal of Medical Science.* 2015;184(2):441-7. doi:10.1007/s11845-014-1140-1.

295. Zhong W, Maradit-Kremers H, St Sauver JL, et al. Age and sex patterns of drug prescribing in a defined American population. *Mayo Clinic Proceedings.* 2013;88(7):697-707. doi:10.1016/j.mayocp.2013.04.021.

296. Gill K, Pande R, Malhotra A. Women deliver for development. *Lancet (London, England).* 2007;370(9595):1347-57. doi:10.1016/s0140-6736(07)61577-3.

297. Bond CA, Raehl CL. Adverse drug reactions in United States hospitals. *Pharmacotherapy.* 2006;26(5):601-8. doi:10.1592/phco.26.5.601.

298. Thomas EJ, Lipsitz SR, Studdert DM, al. e. The reliability of medical record review for estimating adverse event rates. *Annals of Internal Medicine.* 2002;136(11):812-6.

299. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: Systematic analysis of population health data. *Lancet*. 2006;367(9524):1747-57. doi:10.1016/s0140-6736(06)68770-9.

300. World Health Organisation. Tuberculosis progress in Ethipia. Via http://www.afro.who.int/en/ethiopia/country-programmes/topics/4481-tuberculosis.html. Accessed on 24 June 2017.

301. Wang H, Wolock TM, Carter A, et al. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980-2015: The global burden of disease study 2015. *The lancet. HIV*. 2016;3(8):e361-87. doi:10.1016/s2352-3018(16)30087-x.

302. World Health Organisation. Noncommunicable Diseases (NCD) Country Profiles 2014. Via http://www.afro.who.int/en/ethiopia/country-programmes/topics/4591-ethiopia-non-communicable-diseases-ncd.html. Accessed on 10 Feb 2017 at 9:11am.

303. Mamo Y, Seid E, Adams S, Gardiner A, Parry E. A primary healthcare approach to the management of chronic disease in Ethiopia: an example for other countries. *Clinical Medicine (London, England)*. 2007;7(3):228-31.

304. Gebretekle GB, Serbessa MK. Exploration of over the counter sales of antibiotics in community pharmacies of Addis Ababa, Ethiopia: Pharmacy professionals' perspective. *Antimicrobial Resistance and Infection Control*. 2016;5:2. doi:10.1186/s13756-016-0101-z.

305. Tegegne GT, Gaddisa T , Kefale B, et al. Drug therapy problem and contributing factors among ambulatory hypertensive patients in Ambo General Hospital, West Shoa,Ethiopia. *Global Journal of Medical Research*. 2015;15(4):20-6.

306. Oumer S. Irrational use of medications among elderly patients in an Ethiopian referral hospital. *African Journal of Pharmacy and Pharmacology*. 2017;11(15):191-4,. doi:10.5897/AJPP2017.4736.

307. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Archives of Internal Medicine.* 2008;168(17):1890-6. doi:10.1001/archinternmed.2008.3.

308. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. *European Journal of Clinical Pharmacology.* 2008;64(12):1147-61. doi:10.1007/s00228-008-0553-z.

309. Getahun W, Gedif T, Tesfaye F. Regular Khat (Catha edulis) chewing is associated with elevated diastolic blood pressure among adults in Butajira, Ethiopia: A comparative study. *BMC Public Health.* 2010;10:390. doi:10.1186/1471-2458-10-390.

310. Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. *European Journal of Epidemiology*. 1994;10(4):405-11.

311. Classification Committee of the World Organisation of Family Doctors (WICC) 1998. ICPC-2: International Classification of Primary Care. 2nd edn. Oxford: *Oxford University Press*.1998.

312. Wawruch M, Zikavska M, Wsolova L, et al. Adverse drug reactions related to hospital admission in Slovak elderly patients. *Archives of Gerontology and Geriatrics.* 2009;48(2):186-90. doi:10.1016/j.archger.2008.01.004.

313. Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: Misleading, but manageable. *Clinical Interventions in Aging.* 2008;3(2):383-9.

314. Department of health and human services. National heart, lung, and blood institute. Available from: www.nhLbi.nih.gov/health/public/heart/obesity. Accessed on 20 June 2017.

315. Levey AS, Coresh J. Chronic kidney disease. *Lancet.* 2012;379(9811):165-80. doi:10.1016/s0140-6736(11)60178-5.

316. Reuben A. Hy's law. *Hepatology.* 2004;39(2):574-8. doi:10.1002/hep.20081.

317. World Health Organisation. Treatment of Tuberculosis: Guidelines for national programmes. 4th edition. Switzerland, Geneva, World Health Organisation; 2010. Via http://www.who.int/tb/publications/tb_treatmentguidelines/en/.

318. British National Formulary 67 (BNF). Joint formulary committee, Pharmaceutical Press; 2014.

319. Up-To-Date 19.3. Via http://freemedicalresources.blogspot.com.au/ 2012/08/use-uptodate-database-offline-with-your.html.

320. Robin X, Turck N, Hainard A, et al. pROC: An open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics.* 2011;12:77. doi:10.1186/1471-2105-12-77.

321. Belachew T. Are we ready for the rising silent epidemic of metabolic syndrome and chronic non-communicable disease in Ethiopia? *Ethiopian Journal of Health Sciences.* 2015;25(1):1-2.

322. AIDS resource centre. Via http://www.etharc.org/index.php/resources/healthstat/hivaids-estimates-and-projections-in-ethiopia-2011-2016. Accessed on 09 January 2017.

323. Sharif-Askari FS, Syed Sulaiman SA, Saheb Sharif-Askari N, Al Sayed Hussain A. Development of an adverse drug reaction risk assessment score among hospitalized patients

with chronic kidney disease. *PLoS One.* 2014;9(4):e95991. doi:10.1371/journal.pone.0095991.

324. Corsonello A, Onder G, Bustacchini S, et al. Estimating renal function to reduce the risk of adverse drug reactions. *Drug Safety.* 2012;35 Suppl 1:47-54. doi:10.1007/bf03319102.

325. Zeeh J, Platt D. The aging liver: Structural and functional changes and their consequences for drug treatment in old age. *Gerontology.* 2002;48(3):121-7. doi:52829.

326. Manley HJ, McClaran ML, Overbay DK, et al. Factors associated with medication-related problems in ambulatory hemodialysis patients. *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation.* 2003;41(2):386-93. doi:10.1053/ajkd.2003.50048.

327. Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in Europe: A review of recent observational studies. *Drug Safety.* 2015;38(5):437-53. doi:10.1007/s40264-015-0281-0.

328. Ali EE. Health care financing in Ethiopia: Implications on access to essential medicines. *Value in Health Regional Issues.* 2014;4:37-40.Via http://www.valuehealthregionalissues.com/article/S2212-1099%2814%2900049-1/pdf Accessed on 22 June 2017 at 4:53pm.

329. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Diseases.* 1987;40(5):373-83.

330. Michael JA, Sandra LKG, Pamela LS, Ananth MA, Amy LS. Comparing drug-drug interaction severity ratings between bedside clinicians and proprietary databases, ISRN critical care. *Hindawi.* 2013;2013:1-6. doi:10.5402/2013/347346.

331. Zargarzadeh AH, Emami MH, Hosseini F. Drug-related hospital admissions in a generic pharmaceutical system. *Clinical and Experimental Pharmacology & Physiology*. 2007;34(5-6):494-8. doi:10.1111/j.1440-1681.2007.04600.x.

332. Tourret J, Deray G, Isnard-Bagnis C. Tenofovir effect on the kidneys of HIV-infected patients: A double-edged sword? *Journal of the American Society of Nephrology : JASN.* 2013;24(10):1519-27. doi:10.1681/asn.2012080857.

333. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: Renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America.* 2010;51(5):496-505. doi:10.1086/655681.

334. Mulenga L, Musonda P, Mwango A, et al. Effect of baseline renal function on tenofovir-containing antiretroviral therapy outcomes in Zambia. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America.* 2014;58(10):1473-80. doi:10.1093/cid/ciu117.

335. Leone R, Sottosanti L, Luisa Iorio M, et al. Drug-related deaths: An analysis of the Italian spontaneous reporting database. *Drug Safety*. 2008;31(8):703-13.

336. Huang YS, Chern HD, Su WJ, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. Hepatology. 2002;35(4):883-9. doi:10.1053/jhep.2002.32102

337. Huang YS, Chern HD, Su WJ, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. *Hepatology.* 2002;35(4):883-9. doi:10.1053/jhep.2002.32102.

338. Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: Concise up-to-date review. *Journal of Gastroenterology and Hepatology.* 2008;23(2):192-202. doi:10.1111/j.1440-1746.2007.05207.x.

339. Fernandez-Villar A, Sopena B, Fernandez-Villar J, et al. The influence of risk factors on the severity of anti-tuberculosis drug-induced hepatotoxicity. *The International Journal of Tuberculosis and Lung Disease : The Official Journal of the International Union Against Tuberculosis and Lung Disease.* 2004;8(12):1499-505.

340. Chaponda M, Pirmohamed M. Hypersensitivity reactions to HIV therapy. *British Journal of Clinical Pharmacology*. 2011;71(5):659-71. doi:10.1111/j.1365-2125.2010.03784.x.

341. Lee WM. Drug-induced hepatotoxicity. The New England journal of medicine. 1995;333(17):1118-27. doi:10.1056/nejm199510263331706.

342. Bjornsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. Digestive and Liver Disease : Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2006;38(1):33-8. doi:10.1016/j.dld.2005.06.004.

343. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology.* 2002;36(2):451-5. doi:10.1053/jhep.2002.34857.

344. Council for International Organizations of Medical Sciences. Working group on drug induced liver injury. *Geneva. Council for International Organisations of Medical Sciences.* 2017. Via https://cioms.ch/working_groups/dili/.

345. Norris W, Paredes AH, Lewis JH. Drug-induced liver injury in 2007. *Current Opinion in Gastroenterology.* 2008;24(3):287-97. doi:10.1097/MOG.0b013e3282f9764b.

346. Takikawa H. Recent status of drug-induced liver injury. *Hepatology Research : The Official Journal of The Japan Society of Hepatology.* 2009;39(1):1-6. doi:10.1111/j.1872-034X.2008.00400.x.

347. Hayashi PH, Chalasani NP. Increasing impact of drug-induced liver injury. *Clinical Liver Disease.* 2015;5(6):136-8.

348. Devarbhavi H. An Update on Drug-induced Liver Injury. *Journal of Clinical and Experimental Hepatology.* 2012;2(3):247-59. doi:10.1016/j.jceh.2012.05.002.

349. Hussaini SH, O'Brien CS, Despott EJ, Dalton HR. Antibiotic therapy: A major cause of drug-induced jaundice in southwest England. *European Journal of Gastroenterology & Hepatology.* 2007;19(1):15-20. doi:10.1097/01.meg.0000250581.77865.68.

350. Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: Causes, outcome, prognosis, and predictors of mortality. *The American Journal of Gastroenterology*. 2010;105(11):2396-404. doi:10.1038/ajg.2010.287.

351. Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Annals of Internal Medicine.* 2002;137(12):947-54.

352. Idilman R, Bektas M, Cinar K, et al. The characteristics and clinical outcome of drug-induced liver injury: A single-center experience. *Journal of Clinical Gastroenterology*. 2010;44(6):e128-32. doi:10.1097/MCG.0b013e3181c5e9cc.

353. Friis H, Andreasen PB. Drug-induced hepatic injury: An analysis of 1100 cases reported to the Danish Committee on adverse drug reactions between 1978 and 1987. *Journal of Internal Medicine.* 1992;232(2):133-8.

354. Andrade RJ, Robles M, Fernandez-Castaner A, Lopez-Ortega S, Lopez-Vega MC, Lucena MI. Assessment of drug-induced hepatotoxicity in clinical practice: A challenge for gastroenterologists. *World Journal of Gastroenterology.* 2007;13(3):329-40.

355. Chen M, Suzuki A, Borlak J, Andrade RJ, Lucena MI. Drug-induced liver injury: Interactions between drug properties and host factors. *Journal of Hepatology.* 2015;63(2):503-14. doi:10.1016/j.jhep.2015.04.016.

356. Ortega-Alonso A, Stephens C, Lucena MI, Andrade RJ. Case characterization, clinical features and risk factors in drug-induced liver injury. *International Journal of Molecular Sciences.* 2016;17(5). doi:10.3390/ijms17050714.

357. Tajiri K, Shimizu Y. Practical guidelines for diagnosis and early management of drug-induced liver injury. *World Journal of Gastroenterology.* 2008;14(44):6774-85.

358. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. *Clinical Pharmacology and Therapeutics.* 2011;89(6):806-15. doi:10.1038/clpt.2011.58.

359. De Valle MB, Av Klinteberg V, Alem N, Olsson R, Bjornsson E. Drug-induced liver injury in a Swedish University hospital out-patient hepatology clinic. *Alimentary Pharmacology & Therapeutics.* 2006;24(8):1187-95. doi:10.1111/j.1365-2036.2006.03117.x.

360. Woo HJ, Kim HY, Choi ES, et al. Drug-induced liver injury: A 2-year retrospective study of 1169 hospitalized patients in a single medical center. *Phytomedicine : International Journal of Phytotherapy and Phytopharmacology*. 2015;22(13):1201-5. doi:10.1016/j.phymed.2015.10.002.

361. Sobhonslidsuk A, Poovorawan K, Soonthornworasiri N, Pan-Ngum W, Phaosawasdi K. The incidence, presentation, outcomes, risk of mortality and economic data of drug-induced liver injury from a national database in Thailand: A population-base study. *BMC Gastroenterology.* 2016;16(1):135. doi:10.1186/s12876-016-0550-0.

362. Wondwossen A, Waqtola C, Gemeda A. Incidence of antituberculosis-drug-induced hepatotoxicity and associated risk factors among tuberculosis patients in Dawro Zone, South Ethiopia: A cohort study. *International Journal of Mycobacteriology.* 2016;5(1):14-20. doi:10.1016/j.ijmyco.2015.10.002.

363. Yimer G, Gry M, Amogne W, et al. Evaluation of patterns of liver toxicity in patients on antiretroviral and anti-tuberculosis drugs: A prospective four arm observational study in ethiopian patients. *PLoS One.* 2014;9(4):e94271. doi:10.1371/journal.pone.0094271

364. Bjornsson E, Jacobsen EI, Kalaitzakis E. Hepatotoxicity associated with statins: Reports of idiosyncratic liver injury post-marketing. *Journal of Hepatology.* 2012;56(2):374-80. doi:10.1016/j.jhep.2011.07.023.

365. World Health Organisation. Treatment of tuberculosis: Guidelines for treatment of drug-susceptible tuberculosis and patient care update. *Switzerland, World Health Organisation;* 2017. p. 13-5.

366. Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. *American Journal of Respiratory and Critical Care Medicine.* 2002;166(7):916-9. doi:10.1164/rccm.2108091.

367. Shakya R, Rao BS, Shrestha B. Incidence of hepatotoxicity due to antitubercular medicines and assessment of risk factors. *Annals of Pharmacotherapy*. 2004;38(6):1074-9. doi:10.1345/aph.1D525.

368. Parris M. Kidd. Glutathione: Systemic protectant against oxidative and ree radical damage. Via http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.372.839&rep=rep1&type=pdf.

369. Pirmohamed M, Naisbitt DJ, Gordon F, Park BK. The danger hypothesis: Potential role in idiosyncratic drug reactions. *Toxicology.* 2002;181-182:55-63.

370. Ramappa V, Aithal GP. Hepatotoxicity related to anti-tuberculosis drugs: Mechanisms and management. *Journal of Clinical and Experimental Hepatology.* 2013;3(1):37-49. doi:10.1016/j.jceh.2012.12.001.

371. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: A 7-year survey from a public health tuberculosis clinic. *Journal of American Medical Association.* 1999;281(11):1014-8.

372. Warmelink I, ten Hacken NH, van der Werf TS, van Altena R. Weight loss during tuberculosis treatment is an important risk factor for drug-induced hepatotoxicity. *The British Journal of Nutrition*. 2011;105(3):400-8. doi:10.1017/s0007114510003636.

373. Buchanan N, Eyberg C, Davis MD. Isoniazid pharmacokinetics in kwashiorkor. *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde.* 1979;56(8):299-300.

374. Walter-Sack I, Klotz U. Influence of diet and nutritional status on drug metabolism. *Clinical Pharmacokinetics.* 1996;31(1):47-64. doi:10.2165/00003088-199631010-00004.

375. Fetene N, Linnander E, Fekadu B, et al. The Ethiopian health extension program and variation in health systems performance: What matters? *PLoS One.* 2016;11(5):e0156438. doi:10.1371/journal.pone.0156438

376. Kebede AH, Alebachew Z, Tsegaye F, Lemma E, Abebe A, Agonafir M, et al. The first population-based national tuberculosis prevalence survey in Ethiopia, 2010-2011. *The International Journal of Tuberculosis and Lung Disease : The Official Journal of the International Union Against Tuberculosis and Lung Disease.* 2014;18(6):635-9.

377. Federal Ministry of Helath.Tuberculosis, Leprosy and TB/HIV Prevention and Control Program Manual. Addis Ababa: 2008.Via http://www.who.int/hiv/pub/guidelines/ethiopia_tb.pdf.

378. Gesesew H, Tsehaineh B, Massa D, Tesfay A, Kahsay H, Mwanri L. The prevalence and associated factors for delayed presentation for HIV care among tuberculosis/HIV co-infected patients in Southwest Ethiopia: A retrospective observational cohort. *Infectious Diseases of Poverty.* 2016;5(1):96. doi:10.1186/s40249-016-0193-y.

379. Mitku AA, Dessie ZG, Muluneh EK, Workie DL. Prevalence and associated factors of TB/HIV co-infection among HIV Infected patients in Amhara region, Ethiopia. *African Health Sciences.* 2016;16(2):588-95. doi:10.4314/ahs.v16i2.29.

380. Gaude GS, Chaudhury A, Hattiholi J. Drug-induced hepatitis and the risk factors for liver injury in pulmonary tuberculosis patients. *Journal of Family Medicine and Primary Care*. 2015;4(2):238-43. doi:10.4103/2249-4863.154661.

381. Mulu H, Hamza L, Alemseged F. Prevalence of malnutrition and associated factors among hospitalized patients with acquired immunodeficiency syndrome in Jimma University Specialized Hospital, Ethiopia. *Ethiopian Journal of Health Sciences.* 2016;26(3):217-26.

382. Singh J, Garg PK, Tandon RK. Hepatotoxicity due to antituberculosis therapy. Clinical profile and reintroduction of therapy. *Journal of Clinical Gastroenterology.* 1996;22(3):211-4.

383. Golemba AS, Ferreyra FG, Martearena RE, Achinelli FR, Rovai GB. Drug-induced hepatotoxicity and tuberculosis in a hospital from the Argentinian northeast: Cross-sectional study. *Medwave.* 2015;15(4):e6135. doi:10.5867/medwave.2015.04.6135.

384. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. *The European Respiratory Journal.* 1996;9(10):2026-30.

385. Durand F, Bernuau J, Pessayre D, et al. Deleterious influence of pyrazinamide on the outcome of patients with fulminant or subfulminant liver failure during antituberculous treatment including isoniazid. *Hepatology.* 1995;21(4):929-32.

386. Awofeso N. Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment. *Bulletin of the World Health Organization.* 2008;86(3):B-d.

387. Kaona FA, Tuba M, Siziya S, Sikaona L. An assessment of factors contributing to treatment adherence and knowledge of TB transmission among patients on TB treatment. *BMC Public Health.* 2004;4:68. doi:10.1186/1471-2458-4-68.

388. Gudina EK, Teklu AM, Berhan A, et al. Magnitude of Antiretroviral drug toxicity in adult HIV patients in Ethiopia: A cohort study at seven teaching hospitals. *Ethiopian Journal of Health Sciences.* 2017;27(Suppl 1):39-52.

389. Gesesew HA, Ward P, Woldemichael K, Mwanri L. Late presentation for HIV care in Southwest Ethiopia in 2003-2015: Prevalence, trend, outcomes and risk factors. *BMC Infectious Diseases.* 2018;18(1):59. doi:10.1186/s12879-018-2971-6.

390. Murphy RA, Sunpath H, Kuritzkes DR, Venter F, Gandhi RT. Antiretroviral therapy-associated toxicities in the resource-poor world: The challenge of a limited formulary. *The Journal of Infectious Diseases.* 2007;196 Suppl 3:S449-56. doi:10.1086/521112.

391. Yunihastuti E, Widhani A, Karjadi TH. Drug hypersensitivity in human immunodeficiency virus-infected patient: Challenging diagnosis and management. *Asia Pacific Allergy*. 2014;4(1):54-67. doi:10.5415/apallergy.2014.4.1.54.

392. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: A collaborative analysis of prospective studies. *Lancet.* 2002;360(9327):119-29.

393. CSA, ICF. Ethiopian Demographic Health Survey 2011, vol. 2012. Addis Ababa and Calverton: Central Statistical Agency (Ethiopia) and ICF International. p. 17–27.

394. Ali E, Woldie M. Reasons and outcomes of admissions to the medical wards of Jimma University Specialized Hospital, Southwest Ethiopia. *Ethiopian Journal of Health Sciences.* 2010;20(2):113-20.

395. Kelley CF, Kitchen CM, Hunt PW, et al. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*. 2009;48(6):787-94. doi:10.1086/597093.

396. Jima YT, Angamo MT, Wabe NT. Causes for antiretroviral regimen change among HIV/AIDS patients in Addis Ababa, Ethiopia. *Tanzania Journal of Health Research.* 2013;15(1):1-9.

397. Pau AK. Antiretroviral therapy-associated serious and life-threatening toxicities. *Current Infectious Disease Reports.* 2003;5(5):429-38.

398. Hartmann M. The side effects of antiretroviral therapy. *Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete.* 2006;57(11):969-74. doi:10.1007/s00105-006-1240-6.

399. Shet A, Antony J, Arumugam K, Kumar Dodderi S, Rodrigues R, DeCosta A. Influence of adverse drug reactions on treatment success: Prospective cohort analysis of HIV-infected individuals initiating first-line antiretroviral therapy in India. *PLoS One*. 2014;9(3):e91028. doi:10.1371/journal.pone.0091028.

400. De Bandt JP. Understanding the pathophysiology of malnutrition for better treatment. *Annales Pharmaceutiques Francaises.* 2015;73(5):332-5. doi:10.1016/j.pharma.2015.03.002.

401. Roque M, Salva A, Vellas B. Malnutrition in community-dwelling adults with dementia (NutriAlz Trial). *The Journal of Nutrition, Health & Aging.* 2013;17(4):295-9. doi:10.1007/s12603-012-0401-9.

402. Smyth RM, Gargon E, Kirkham J, et al. Adverse drug reactions in children: A systematic review. *PLoS One.* 2012;7(3):e24061. doi:10.1371/journal.pone.0024061.

Appendices

Appendix A. Participant information sheet

Private Bay 26 Hobart
Tasmania Australia 7001
Phone (03) 6226 2190
Fax (03) 6226 2870
Email: pharmacy@utas.edu.au

Title: "Adverse Drug Reaction Related Admissions to Jimma University Specialised Hospital, Southwest Ethiopia: Clinical Burdens and Determinants"

You are invited to participate in a research study, conducted by the University of Tasmania, School of Medicine. You are selected as a possible participant in this research because you are 18 years of age or older, and are admitted to a medical ward of the Jimma University Specialised Hospital (JUSH) between 01 May 2015 to 31 August 2016.

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read (or to be read) the following information carefully and discuss it with others if you wish.

NB: This form was used after translation into local languages, Amharic and Afan Oromo, as explained in the methodology.

1. What is the background of this study?

Complications related to medicines are an increasingly important health concern. Detection of these complications (known as 'adverse drug reactions (ADRs)) in hospitals provides an important measure of the burden of drug related morbidity on the healthcare system and also recognition of drug safety as a major public health priority.

2. What is an adverse drug reaction (ADR)?

An adverse drug reaction is a response to a drug which occurs at doses normally used in man. Most are predictable and are known as side effects. Common examples include skin rash caused by antibiotics and drowsiness caused by some anti-allergy medicines.

3. What is the purpose of this study?

This study aims to assess the clinical burden of adverse drug reaction-related hospital admissions; determine the incidence rate of severe and preventable ADRs, and identify risk indicators for ADRs for patients admitted in medical wards in Ethiopia. The hope is that ADR risk score will be used to help identify people living in the community who have a high chance of ADRs, so that they can receive additional care and attention from healthcare professionals to reduce their chance of ending up in hospital.

This project forms a part of Mulugeta Angamo's PhD thesis.

4. What does this study involve?

If you agree to participate in this study, you can indicate that you want to be involved in using the attached Participant Consent Form. The study will be conducted over 12 months from 01 May 2015 to 31 August 2016.

This study consists of two parts. Firstly you will be interviewed with a short questionnaire regarding any recent changes to your drug therapy, how you take your medicines, alcohol use, smoking status, khat chewing habit and previous ADRs. The interview will last not more than 30 minutes. Secondly, your medical records at the Jimma University Specialized Hospital (JUSH) will be reviewed to determine whether you experienced an ADR and what factors contributed to any ADR that may have occurred.

5. What are the risks associated with these procedures?

You are unlikely to experience any discomfort during this procedure. If you experience some discomfort during the interview process, it may be due to the following reasons

a) Possible discomfort due to the underlying medical condition.

b) Possible discomfort due to not understanding clearly the scientific reasons for the questions being asked.

c) Discomfort trying to remember the events before admission or medication history asked about by the research officer.

If you find that you are becoming distressed during the interview, you are free to either end the interview or ask the researcher to move the discussion in another direction. If necessary, we will arrange for you to see a counsellor at no expense to you.

6. What are the benefits of this study?

Your participation may contribute to a better understanding of ADRs occurring in adults and elderly people. This may lead to future improvements in ADR prediction for people like you, with the aim of reducing the risks of ADRs for these people. This study also assists health practitioners to identify people who are at increased risk of ADRs and promote safer use of medicines, with a subsequent reduction in the associated costs of admissions due to ADRs or prolongation of hospital stay.

7. What happens if I don't want to take part in the study?

Participation is entirely voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect your future care.

8. How will my confidentiality be protected?

Of the people treating you, only the research pharmacist will know whether or not you are participating in this study. All information will be treated in a confidential manner and all data, including your personal information, will be coded against a unique identifying number so your personal information will be protected. Your name and any other personal information will not be used in reports or publications resulting from this study. All of the information collected as part of this research will be kept in secure storage in the School of Medicine and will be destroyed after a period of 10 years in line with University of Tasmania regulations.

9. Will I benefit from the study?

This study aims to further medical knowledge and may prevent adult and elderly people experiencing ADRs in the future; however, it may not directly benefit you.

10. What should I do if I want to discuss this study further before I decide?

When you have read this information, if you have any queries regarding this study or your participation in this study, please do not hesitate to contact one of the study investigators listed below:

Mulugeta Angamo (PhD candidate)

Telephone: 04 ; Email: mulugeta.angamo@utas.edu.au

Professor Luke Bereznicki (Deputy Head, School of Medicine)

Telephone: 04 ; Email: Luke.Bereznicki@utas.edu.au

Dr Leanne Chalmers (Lecturer, Pharmacy, School of Medicine)

Telephone: 04 ; Email: Leanne.Chalmers@utas.edu.au

Dr Colin Curtain (Pharmacy Practice course coordinator)

Telephone: +61 3 6226 1096; Email: Colin.Curtain@utas.edu.au

Dr Daniel Yilma (Internist, Department of Internal Medicine, Jimma University, Ethiopia)

Telephone: +25 ; Email: @ .com

11. Who should I contact if I have concerns about the conduct of this study?

This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. Please quote the ethics reference number H0014718 and/or RPGC/58/2015.

Thank you for taking the time to consider this study.

If you wish to take part in it, please sign the attached consent form.

This information sheet is for you to keep.

Appendix B. Consent form

Private Bay 26 Hobart
Tasmania Australia 7001
Phone (03) 6226 2190
Fax (03) 6226 2870
Email: pharmacy@utas.edu.au

Title of Project: "Adverse Drug Reaction Related Admissions to Jimma University Specialized Hospital, Southwest Ethiopia: Clinical Burdens and Determinants"

1. I acknowledge that the nature, purpose and contemplated effects of the project so far as it affects me, have been fully explained to my satisfaction by the research worker and my consent is given voluntarily.

2. The details of the project methods have also been explained to me, including the anticipated length of time it will take and an indication of any discomfort, which may be expected. I understand that my involvement means that the research officer has my permission to collect information from my medical records, and that I will be asked to participate in an interview with the research officer.

3. I understand that these are the following risks or possible discomfort:

- Possible discomfort due to the underlying medical condition.
- Possible discomfort due to not understanding clearly the scientific reasons for the questions being asked.
- Discomfort trying to remember the events before admission or medication history asked about by the research officer.

I am aware that if I become distressed during the interview, I may either end the interview or ask the researcher to move the discussion in another direction. If necessary, counselling will be arranged for me at no expense to me.

4. Although I understand that the purpose of this research project is to improve the quality of medical care, it has also been explained that my involvement may not be of any benefit to me.

5. I have been given the opportunity to have a member of my family or friend present while the project was explained to me.

6. I am informed that no information regarding any medical history will be divulged and the results of any analyses involving me will not be published so as to reveal my identity.

7. I understand that my involvement in the project will not affect my relationship with my medical advisers in their management of my health. My withdrawal will not affect my legal rights, my medical care or my relationship with the hospital or my doctors.

8. I understand that I will be given a signed copy of this patient information sheet and consent form. I am not giving up my legal rights by signing this consent form.

9. I understand that the study will be conducted in accordance with the latest versions of the National Statement on Ethical Conduct in Human Research 2007 and applicable privacy laws.

Name of participant_____

Signature of participant _____ Date_____

10. I have explained this project and the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation.

Name of investigator: Mulugeta Angamo

Signature of investigator:_____ Date: _____

Appendix C. Data collection tool

Section I: Socio-demographic and life style characteristics

Patient card number_____

1. Admission date _____(dd/mm/yyyy)
2. Discharge date_____(dd/mm/yyyy)
3. Age_____
4. Gender: a) Male b) Female
5. Weight(Kg) _____
6. Height(m)_____
7. Educational status:
   a) Illiterate
   b) Primary school
   c) Secondary school
   d) College and above
8. Marital status:
   a) Single
   b) Married
   c) Widowed
   d) Divorced
9. Job/ Occupation:
   a) Farmer
   b) Merchant
   c) Government employee
   d) Non-government employee
   e) Private employee
   f) Private technical works (e.g. carpenter)
   g) Retired
   h) Student
   i) Others, specify _____
10. Residence/Place of living:
    a) Rural village
    b) Urban (city or town)
11. Living status
    a) Living with immediate family
    b) Living with extended family

c) Living alone d) Other, specify_____

12. How often do you consume alcohol (Beer, Wine, "Tella","Tejji", "Katikalla", etc)?

a) Usually(daily) d) Not at all

b) Sometimes (2-4 times per week) e) Unknown

c) Rarely (≤1 times per week)

13. Do you smoke cigarette?

a) Yes b) No c) Unknown

If YES, how many cigarette per day _____

14. Khat chewing habit:

a) Regular (≥4 times per week) d) Not chew khat

b) Sometimes (2-3 times per week) e) Unknown

c) Rarely (≤1 times per week)

15. Do you use herbal/alternative medicine in your home or among practitioners?

a) Yes b) No c) Unknown

If YES, the name of the herb/product_____

Section II: Patient's Cognition, daily Activity and Medication adherence (Interviews)

16. Abbreviated Mental Test (AMT): Used for cognitive status assessment

S. No	Questions	Yes=1	No =0
1.	How old are you?		
2.	What is the time (nearest hour)?		
3.	Address for recall at the end of test – this should be repeated by the patient, e.g. Ferenji Arada		
4.	What year is it?		
5.	What is the name of this place?		

6.	Can the patient recognise two relevant persons (e.g. Nurse/Doctor)		
7.	What was the date of your birth?		
8.	When was Ethio-Eritrean War?		
9.	Who is the present Prime Minister?		
10.	Count down from 20 to 1 (no errors, no cues)		
Total Correct sum		_____/10	

NB: A score of less than 7 suggests cognitive impairment.

17. Barthel Index (BI) of Activities of Daily Living

	Variables	With help	Independent
1	Feeding (if food needs to be cut up)	5	10
2	Moving from wheelchair to bed and return (includes sitting up in bed)	5-10	15
3	Personal toilet (wash face, comb hair, shave, clean teeth)	0	5
4	Getting on and off toilet (handling clothes, wipe, flush)	5	10
5	Bathing self	0	5
6	Walking on level surface(or if unable to walk, propel wheelchair) *score only if unable to walk	10 0*	15 5*
7	Ascend and descend stairs	5	10
8	Dressing(includes tying shoes, fastening fasteners)	5	10
9	Controlling bowels	5	10
10	Controlling bladder	5	10
Total Correct sum		_____/100	

Notice: A patient scoring 100 BI is continent, feds himself, dresses himself, gets up out bed and chairs, bathes himself, walks at least a block, and can ascend and descend stairs.

18. Morisky 8-Item Medication Adherence scale

No.	Morisky 8-Item Medication Adherence Questionnaire	Answer
1	Do you sometimes forget to take your medicine?	□ Yes □ No
2	People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?	□ Yes □ No
3	Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?	□ Yes □ No
4	When you travel or leave home, do you sometimes forget to bring along your medicine?	□ Yes □ No
5	Did you take all your medicines yesterday?	□ Yes □ No
6	When you feel like your symptoms are under control, do you sometimes stop taking your medicine?	□ Yes □ No
7	Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	□ Yes □ No
8	How often do you have difficulty remembering to take all your medicine?	□ Never/rarely □ Once in a while □ Sometimes □ Usually □ All the time
Total Correct sum		_____/8

Notice: Never/rarely= 0; Once in a while/ Sometimes/Usually/All the time = 1 and Yes=1 and No=0

Section III: Medical and medication related data (Medical Record Review)

19. Chief compliant for current admission is :

_____

20. Pertinent history of present illness:

_____

_____

21. Current physician diagnosis

_____

_____

_____

22. Was the patient following up for chronic care at ambulatory care clinic?

a) Yes b) No c) unknown

23. Was the patient admitted in the last 3 months?

a) Yes b) No c) unknown

If YES, reasons for admission_____ and

Number of admissions_____

24. Does the patient have documented or reported drug allergy/hypersensitivity history, e.g. to Penicillin, Aspirin?

a) Yes b) No c) unknown

If YES, for which drug/agent_____

25. Does the patient have documented or reported ADR history?

a) Yes b) No c) unknown

If YES, for which drug/agent _____

26. Charlson Comorbidity index:

The Charlson Co-Morbidity Index*	**Yes**	**No**	**Classic score**	**Updated**
AIDS			+6	+4
Cerebrovascular disease (excluding hemiplegia)			+1	+0
Chronic respiratory disease (e.g. asthma, COPD, bronchitis)			+1	+1
Congestive heart failure			+1	+2
Connective tissue disease (e.g. SLE, rheumatoid arthritis, scleroderma, Sjogren's disease, osteoarthritis, etc.)			+1	+1
Dementia			+1	+2
Hemiplegia or paraplegia			+2	+2
Any malignancy including Leukaemia and Lymphoma			+2	+2
Myocardial infarction			+1	+0
Peripheral vascular disease			+1	+ 0
Peptic ulcer disease			+1	+ 0
Diabetes mellitus without end organ damage			+1	+ 0
Diabetes mellitus with end organ damage			+2	+1
Mild liver disease (e.g. cirrhosis without portal HT, chronic hepatitis)			+1	+2
Moderate or severe liver disease (e.g. cirrhosis with portal HT +/- variceal bleeding)			+3	+4
Renal diseases			+2	+1
Metastatic solid tumour			+6	+6
Total score:				
Age of patient 1. Age <40 years: 0 points			+0	+0

2. Age 41-50 years: 1 points	+1	+1
3. Age 51-60 years: 2 points	+2	+2
4. Age 61-70 years: 3 points	+3	+3
5. Age 71-80 years: 4 points	+4	+4
6. Age 81-89 years: 5 points	+5	+5
Total score, including age factor		
***Note:** The following comorbid conditions are mutually exclusive: diabetes with chronic complications and diabetes without chronic complications; mild and moderate/sever liver disease; and any malignancy and metastatic solid tumour		

27. Pertinent Laboratory/Biochemical investigation results that could be helpful for ADR diagnosis (write the laboratory investigation result in-front of respective parameters if it was performed as per the patient clinical indication)

Laboratory parameters	Laboratory investigations vs normal reference values	
	At Admission (if any between 0 to 24 hrs of admission)	Reference values (Bases on Koda-Kimble, et al. Applied therapeutics book)
Renal function test		
a) Scr		0.6-1.2mg/dl
b) BUN		8-18 mg/dl
c) eGFR		75-125ml/min
Liver function test		
a) AST		0-35 IU/L
b) ALT		0-35IU/L

c) ALP		30 – 120 U/L
d) Bilirubin-total		0.1–1.0 mg/dL
e) Bilirubin-direct		0-0.2mg/dL
f) Serum albumin		3.5 – 5 g/dL
Complete Blood Count(CBC)		
a) WBC count		3.2-9.8x10^3cell/mm^3
b) RBC count		4.2-5.9x10^6 for M&3.5-5x10^6 cells/mm^3 forF
c) Neutrophils		54%-62%
d) Bands		3%-5%
e) Lymphocytes		25%-33%
f) Monocytes		3%-7%
g) Eosinophils		1%-3%
h) Basophils		<1%
i) Hgb		14-18g/dL for M &12-16 g/dL for females
j) HCT		39-49% for M &33-43% for F
k) MCV		76 to 100 μm^3
l) MCH		27 to 33pg
m) MCHC		33- 37g/dL
n) PLT		130-400x10^3/ mm^3
Coagulation Test		
a) INR		2.0-3.0 for AF/DVT/VHD
b) aPTT		35 to 45 to seconds
Lipid panel		

a) TG		<160 mg/dL
b) Total Cholest		<200 mg/dL
c) LDL		70–160 mg/dL
d) HDL		>45 mg/dL
Cardiac function		
a) Troponin I		<0.03 ng/mL
b) CK-MB		0–12 units/L
Electrolyte test		
a) Na+		135 - 145 mEq/L
b) K+		3.5 – 5.0 mEq/L
c) Ca+		8.8 – 10.2 mg/dl
Glycaemic level		
a) FPG		70 – 110 mg/dl
b) RPG		140-180mg/dl
Vital signs		
a) Temperature		
b) BP		
c) PR		
d) RR		
Ultrasonography interpretation		

ECHO interpretation		
EKG interpretation		
Others		

28. List of medications (including OTC medications and contraceptive pills) used **prior to the current hospital admissions**

Name of the prescription only drug □ Yes □ No	Dose	Frequency	Date started	Date stopped	Routes	Remark
1.						
2.						
3.						
4.						
5.						
6.						
7.						
Name of Contraceptives □ Yes □ No	Dose	Frequency	Date started	Date stopped	Routes	Remark
8.						
9.						
Name of OTC drugs □ Yes □ No	Dose	Frequency	Date started	Date stopped	Routes	Remark
10.						
11.						
12.						

Section IV: Summary of ADR Case note

29. Describe the suspected adverse reactions based on the above available patient data.

30. What are the pertinent clinical and laboratory abnormalities for suspected corresponding drug(s)?

Pertinent suspected drug related reactions (after interviewing of patient and reviewing of patient medical record) i.e. before causality assessment: **Clinical data**	Pertinent **biochemical /laboratory** abnormality detected	Corresponding suspected list of drug(s) patient taking at admission
1)		
2)		
3)		
4)		

31. Suspected drug outcomes

a) Drug stopped

b) Drug withheld

c) Drug continued

d) Drug substituted

e) Dose reduced

f) Antidote or counteracting agent administered

g) Unknown

32. ADR outcome:

a) Fatal

b) Not yet recovered

c) Partially recovered

d) Recovered

e) Unknown

Section V: <u>ADR Causality, Severity, Type and Preventability assessment</u>

33. Causality assessment for each of the suspected drug on Q30 above

Question	**Yes**	**No**	**Do Not Know**	**Scores for suspected drug(s) in Q31**			
				(1)	**(2)**	**(3)**	**(4)**
1. Are there previous conclusive reports on this reaction?	+1	0	0				
2. Did the adverse reaction appear after the suspected drug was administered?	+2	-1	0				
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0				

4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0				
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0				
6. Did the reaction reappear when a placebo was given?	-1	+1	0				
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0				
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0				
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0				
10. Was the adverse reaction confirmed by any objective evidence?	+1	0	0				
Total Score:							

34. List of drug(s) implicated in causing ADR

List of drug(s)	List of corresponding ADRs
1)	
2)	
3)	
4)	

35. Type of ADR based on Rawlins classification (Tick "√" in the most appropriate box taking into consideration of ADR listed in Q34)

ADR type	Reaction (1)	Reaction (2)	Reaction (3)	Reaction (4)
a) Type A (Dose dependent, pharmacological and predictable)				
b) Type B (Dose independent, bizarre and non-predictable)				

36. Is there clinically significant interactions between or among drugs used by the patient at admission? This question should be answered by checking interactions in MICROMEDEX drug interaction checker and based on existing evidences.

a) Yes b) No c) Unknown

If YES, the severity level of interaction is:

a) **Contraindicated** (Avoid combination)-means the drugs are contraindicated for concurrent use

b) **Major** (Consider therapy modification) -means the interaction may be life threatening and/or require medical intervention to minimise or prevent serious adverse events

c) **Moderate** (Monitor therapy)-means the interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy

d) **Minor** (No action is needed) – means the interaction would have limited clinical effects. May include an increase in the frequency or severity of the side effects, but generally it would not require a major alteration in therapy

e) **Unknown** (No known interaction)-the interaction is unknown

37. Severity of ADR based on modified Hartwig and Siegel scale (Tick √ in the most appropriate level for ADR listed in Q34)

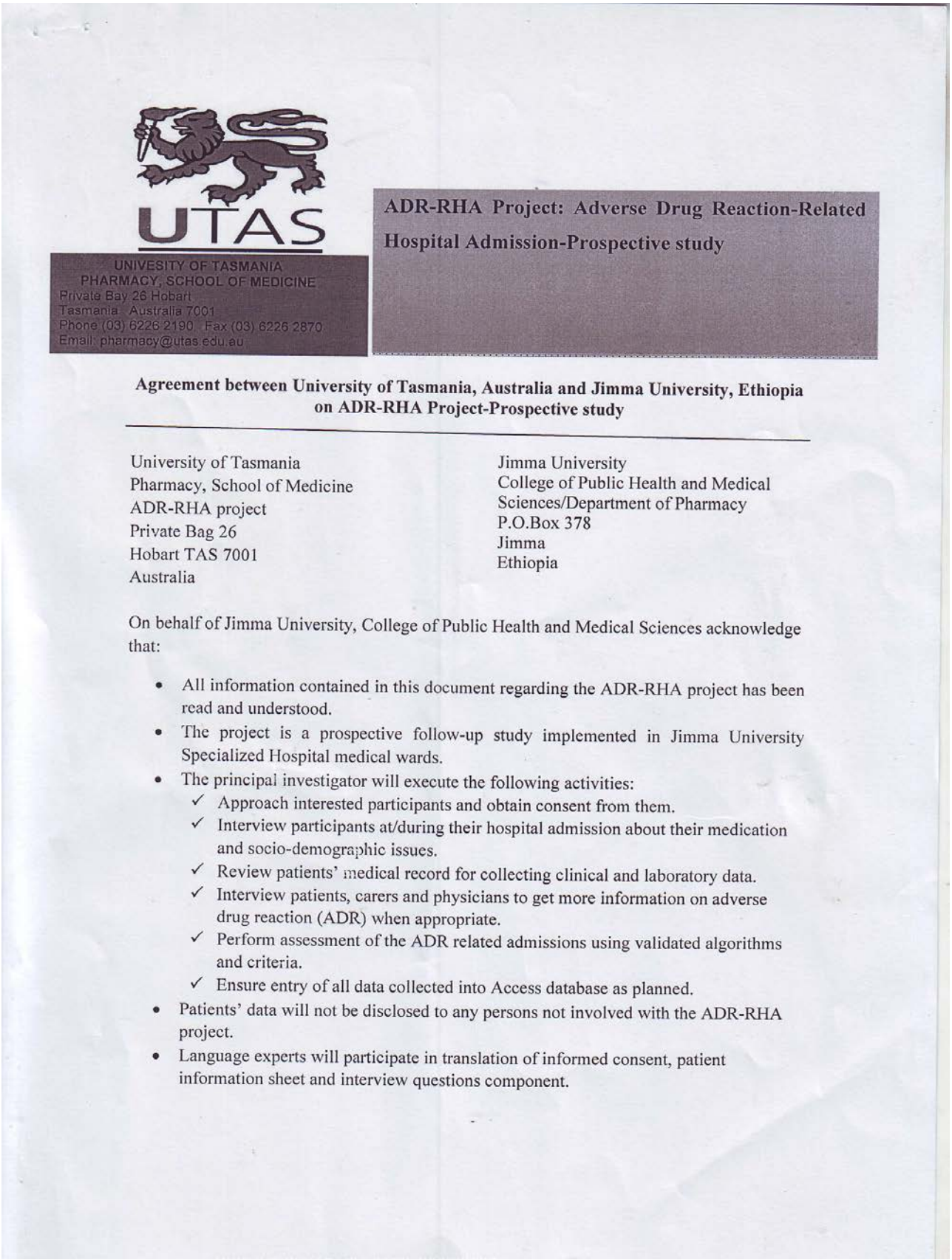
Severity scale	Severity Level	Description of the above identified reaction(s)	Reaction (1)	Reaction (2)	Reaction (3)	Reaction (4)
a) Mild	Level 1	The ADR requires no change in treatment with the suspected drug. □ Yes □ No				
	Level 2	The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. □ Yes □ No				
b) Moderate	Level 3	The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/ or an antidote or other treatment is required. There is no increase in length of stay. □ Yes □ No				
	Level 4 (a)	Any level 3 ADR that increases length of stay by at least one day. □ Yes □ No				
	Level 4 (b)	The ADR is the reason for admission. □ Yes □ No				
c) Severe	Level 5	Any level 4 ADR that requires intensive medical care. □ Yes □ No				
	Level 6	The ADR causes permanent harm to the patient. □ Yes □ No				
	Level 7(a)	The ADR directly leads to the death of the patient. □ Yes □ No				
	Level 7(b)	The ADR indirectly leads to the death of the patient. □ Yes □ No				

38. Preventability of ADR based on Schumock and Thornton scale (Tick √ in the most appropriate preventability scale bases on the ADR listed in Q 34). Notice: Answering "yes" to one or more of the questions in section "a" implies that an ADR is DEFINITELY preventable and If answers are all negative to section "a", then proceed to Section "b". Answering "yes" to one or more of the questions in section "b" implies that an ADR is PROBABLY preventable and if the answers are all negative to section "b", then proceed to Section "c". In Section "c" the ADR is NOT preventable

Preventability scale	Description of each scale	Reaction (1)	Reaction (2)	Reaction (3)	Reaction (4)
a. Definitely Preventable	1. Was there a history of allergy or previous reactions to the drug? □ Yes □ No 2. Was the drug involved inappropriate for the patient's clinical condition? □ Yes □ No 3. Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state? □ Yes □ No 4. Was a toxic serum drug concentration (or laboratory monitoring test) documented? □ Yes □ No				

	5. Was there a known treatment for the adverse drug reaction? □ Yes □ No				
b. Probably Preventable	6. Was required therapeutic drug monitoring or other necessary laboratory tests not performed? □ Yes □ No 7. Was a drug interaction involved in the ADR? □ Yes □ No 8. Was poor compliance involved in the ADR? □ Yes □ No 9. Were preventative measures not prescribed or administered to the patient? □ Yes □ No				
c. Not preventable	If all above criteria not fulfilled				

Appendix D. Agreement between University of Tasmania and Jimma University



UTAS

UNIVESITY OF TASMANIA
PHARMACY, SCHOOL OF MEDICINE
Private Bay 26 Hobart
Tasmania Australia 7001
Phone (03) 6226 2190 Fax (03) 6226 2870
Email: pharmacy@utas.edu.au

ADR-RHA Project: Adverse Drug Reaction-Related Hospital Admission-Prospective study

Agreement between University of Tasmania, Australia and Jimma University, Ethiopia on ADR-RHA Project-Prospective study

University of Tasmania
Pharmacy, School of Medicine
ADR-RHA project
Private Bag 26
Hobart TAS 7001
Australia

Jimma University
College of Public Health and Medical Sciences/Department of Pharmacy
P.O.Box 378
Jimma
Ethiopia

On behalf of Jimma University, College of Public Health and Medical Sciences acknowledge that:

- All information contained in this document regarding the ADR-RHA project has been read and understood.
- The project is a prospective follow-up study implemented in Jimma University Specialized Hospital medical wards.
- The principal investigator will execute the following activities:
  - ✓ Approach interested participants and obtain consent from them.
  - ✓ Interview participants at/during their hospital admission about their medication and socio-demographic issues.
  - ✓ Review patients' medical record for collecting clinical and laboratory data.
  - ✓ Interview patients, carers and physicians to get more information on adverse drug reaction (ADR) when appropriate.
  - ✓ Perform assessment of the ADR related admissions using validated algorithms and criteria.
  - ✓ Ensure entry of all data collected into Access database as planned.
- Patients' data will not be disclosed to any persons not involved with the ADR-RHA project.
- Language experts will participate in translation of informed consent, patient information sheet and interview questions component.

- All the non-consumable materials (printer and body mass index measuring instrument) will be owned by the respective department at the completion of the project.
- Some necessary support (e.g. office, desk, internet access) will be provided to the investigator.

The ADR-RHA project in University of Tasmania, Pharmacy, School of Medicine agrees to:

- Transfer **$1600.00 AUD** to Jimma University for covering costs incurred in implementing the ADR-RHA project such as:
  - ✓ Purchasing a laser jet printer for the study.
  - ✓ Purchasing printer colours.
  - ✓ Purchasing consumable stationary items (paper, pen, etc).
  - ✓ Buying body mass index measuring instrument and
  - ✓ Other necessary costs
- Maintain the confidentiality of all the data that is collected.
- All patients' specific information will be de-identified before analysis.
- Any publication that arises from this work will not include any information that will enable identification of individual patients, data collectors and others involved in the project.
- All data collected by data collectors will be transferred to the School of Medicine (Pharmacy Division) on completion of the data collection and will only be accessible to researchers for research purposes.
- All research data will be securely stored on the University of Tasmania premises and will be destroyed when no longer required.

Signed: [redacted]

Date: 21/04/2015

Name [redacted]

College of Public Health and Medical Sciences,
Jimma University,Phone+251 471 110331,
Fax +251471 114484

Date: 25th March 2015

Signed: [redacted]

Luke Bereznicki
Deputy Head, School of Medicine
University of Tasmania
Phone (03) 6226 2190 Fax (03) 6226 2870

⇒ Account Name : [redacted]
Account Number :
Bank Name :
Branch Name :
SWIFT CODE :

Appendix E. Ethics approval letters

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

16 April 2015

AssocProf Luke Bereznicki
C/- School of Medicine (Pharmacy)

Sent via email

Dear AssocProf Bereznicki

REF NO: H0014718
TITLE: Adverse Drug Reaction Related Admissions to Jimma University Specialized Hospital, Southwest Ethiopia: Clinical Burdens and Determinants

Document	*Version*	*Date*
PROTOCOL	-	February 2015
NEAF	Version 2	-
Information Sheet	Version 1	16 February 2015
Consent Form	Version 1	16 February 2015
Data Collection Tool (Patient Interview components) Section I	Version 1	16 February 2015
Section II: Patient's Cognition, daily Activity and Medication adherence	Version 1	16 February 2015

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above documentation on **09 April 2015** to be conducted at the following site(s):

Jimma University Specialized Hospital, Jimma, Oromia, Southwest Ethiopia (Local approval required)

Please ensure that all investigators involved with this project have cited the approved versions of the documents listed within this letter and use only these versions in conducting this research project.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approvals of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2014).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC. Please note that all requests for changes to approved documents must include a version number and date when submitted for review by the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested.
http://www.research.utas.edu.au/human_ethics/medical_forms.htm

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

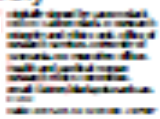
(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for 4 years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due **09 April 2016.** You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Yours sincerely



Lauren Black
Executive Officer, Health and Medical Human Research Ethics Committee
Research Integrity and Ethics Unit
Office of Research Services
University of Tasmania
Private Bag 01
Hobart Tas 7001
T +61 3 6226 2764

JIMMA UNIVERSITY
ጅማ ዩኒቨርሲቲ

ቁጥር Ref.No. RPGC/58/2015
ቀን Date 4/05/2015

Institutional Review Board (IRB),
College of Health Sciences,
JU, Jimma
Tel: +251471120945
E-mail: mirkuzie.woldie@ju.edu.et

To Mulugeta Angamo

Subject: Ethical clearance of your research protocol

The IRB of College of Health Sciences has reviewed your research protocol on expedited manner.

"Adverse drug recaction-related admissions to Jimma University Specialized Hospital, Southwest Ethiopia: Clinical burden and determinants"

This research protocol as presented to the IRB meets the ethical and scientific standards outlined in the national and international guidelines. Hence, we are pleased to inform you that your protocol is *ethically cleared.*

We strongly recommend that any significant deviation from the methodological details indicated in the approved protocol must be communicated to the IRB before they are implemented.

With regards,

Mirkuzie W(PH)
Research & Post Graduate
Coordinator

Appendix F. ADR preventability factors

Of 119 ADR-related admissions, 106 (89.1%) ADRs in 92 patients were suspected to be preventable according to Schumock et al. preventability assessment criteria. The leading preventability factors identified were inadequate monitoring of therapies (73.3%), presence of drug interactions (65.0%), not prescribing preventive measures (58.3%), presence of poor medication compliance (30.5%) and presence of previous ADR history (24.4%) (Fig 1). The majority (75.5%) of the reactions involved >1 Schumock et al. preventability assessment factor.

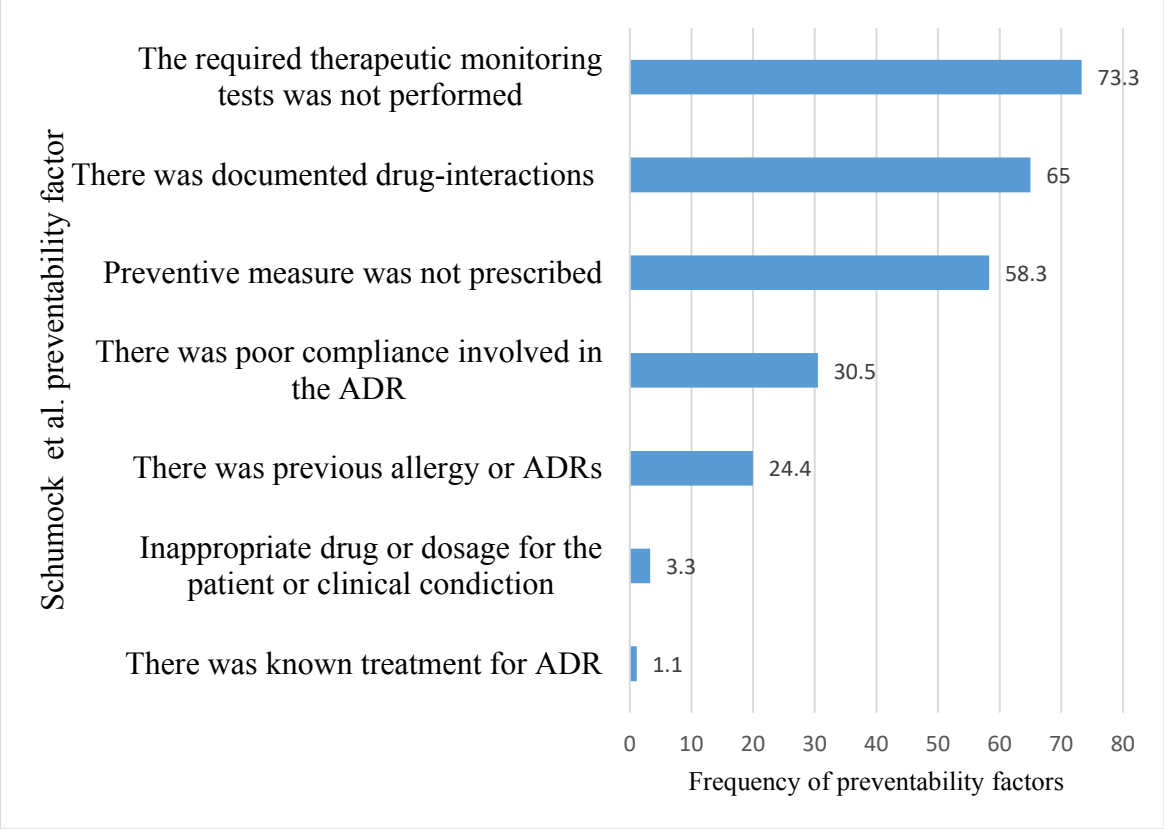


Figure 1. Schumock et al. preventability factors of ADR-related hospitalisation

Appendix G. ADR severity, outcomes and length of hospital stay

According to the Hartwig severity scale, 95 (79.8%) of the ADRs were reasons for hospital admission and/or increased LOS by at least one day, 6 (5.0%) of the ADRs required intensive medical care, 3 (2.5%) caused permanent harm to the patient and 15 (12.6%) led to death directly or indirectly. Of the 119 ADRs, 58 (48.7%) were not recovered at discharge whereas 46 (38.7%) ADR cases were fully recovered (Table 1).

One hundred and nineteen ADRs resulted in 1,565 hospital days (1,319 days for moderate ADRs and 246 days for severe ADRs), which was 11.6% of overall admissions (i.e. 13,520 days). The overall median (IQR) LOS for patients with ADRs was 12 (9-20) days. The median (IQR) LOS was shorter for patients with severe ADRs than patients with moderate ADRs and patients without ADRs, 10 (4.5-12) days versus 13 (9-21) days versus 11 (8-16) days, respectively. Overall, ADRs prolonged hospital stay by approximately two days.

Appendix G Table. Hartwig severity scale and outcomes of the patients hospitalised with ADRs

ADR severity level	N (%)
ADR was a reason for hospital admission and/or increased LOS by at least one day	95 (79.8)
ADR that required intensive medical care	6 (5.0)
ADR caused permanent harm to the patient	3 (2.5)
ADR directly or indirectly led to death	15 (12.6)
ADR outcomes	
Fatal	15 (12.6)
Not fully recovered	58 (48.7)
Fully recovered	46 (38.7)

Appendix H. Previous ADR history

Of 1,001 patients included in this study, 41 (4.1%) patients had a previous ADR history. Of these 41 cases, 29 (71.0%) were documented in patients admitted with current ADRs and 61.0% were in females. Of the 29 previous ADR cases identified in patients hospitalised with ADRs, 12 of them were similar in type to the current ADRs. Of 41 patients with a previous ADR history, ADRs were not diagnosed in 12 of them (i.e. 12 patients with previous ADR history were admitted with other medical problems) (Table 2).

Appendix H Table. Case details of patients with previous ADR history

Patient ID	Age	Gender	Previous ADR type/allergy or suspected drug	Current ADR and suspected ADR
07	27	F	Ampicillin suspected allergy	Cloxacillin suspected skin rash
87	58	F	Glibenclamide suspected hypoglycemia	Glibenclamide suspected gastritis
130	27	F	AZT/3TC/EFV with unidentified ADR	Lamivudine suspected diarrhoea
176	50	M	Insulin suspected hypoglycemia	Insulin suspected hypoglycemia
177	48	M	Metoprolol and enalapril with unidentified ADR	Metoprolol suspected syncope
187	40	F	Bleeding with unknown agent	Diclofenac suspected gastrointestinal bleeding
278	36	F	Phenobarbital and phenytoin suspected osteoporosis	Phenobarbital and phenytoin suspected osteomalacia
279	38	M	Anti-TB suspected hepatotoxicity	Isoniazid and pyrazinamide suspected hepatotoxicity
296	75	M	Atorvastatin and aspirin suspected unidentified ADR	Atorvastatin suspected hepatotoxicity
303	25	F	Tenofovir suspected nephrotoxicity	Tenofovir suspected acute kidney injury
304	35	F	Anti-TB suspected skin rash	Isoniazid and rifampicin suspected pruritic skin rash
305	29	F	Efavirenz suspected hepatotoxicity	Efavirenz suspected hepatotoxicity
311	60	M	Lovastatin suspected unidentified ADR	Atorvastatin suspected hepatotoxicity
314	70	M	Glibenclamide suspected hypoglycemia	Insulin and glibenclamide suspected hypoglycemia
340	25	F	Efavirenz suspected nightmare	Efavirenz suspected delirium
345	70	M	Atenolol suspected orthostatic hypotension	Furosemide suspected acute kidney injury and metoprolol suspected vertigo
374	40	F	Skin rash with unknown agent	Isoniazid and pyrazinamide suspected hepatotoxicity
401	27	F	Zidovudine suspected anemia	Nevirapine suspected severe skin rash
405	18	M	Skin rash with unknown agent	Diclofenac suspected acute kidney injury
421	28	F	Anti-TB suspected hepatotoxicity	Isoniazid and pyrazinamide suspected hepatotoxicity
524	37	F	Zidovudine suspected allergic reaction	Rifampicin suspected diarrhea
550	24	M	Anti-TB suspected hepatotoxicity	Isoniazid and pyrazinamide suspected hepatotoxicity
659	55	F	Anti-TB suspected unidentified ADR	Isoniazid and efavirenz suspected hepatotoxicity
677	28	F	Co-trimoxazole suspected hypersensitivity reaction	Isoniazid, pyrazinamide and efavirenz suspected hepatotoxicity

Case details of patients with previous ADR-history cont….

Patient ID	Age	Gender	Previous ADR type/allergy and suspected drug	Current ADR
769	33	M	Anti-TB suspected unidentified ADR	Isoniazid and ritonavir suspected hepatotoxicity
878	25	M	Efavirenz suspected neuropsychiatric problem	Efavirenz suspected delirium
899	35	F	Medroxyprogesterone acetate suspected skin rash	Medroxyprogesterone acetate suspected vaginal bleeding
921	40	F	Hydrochlorothiazide suspected Skin rash	Furosemide suspected acute kidney injury and hypocalcemia
993	19	F	Phenytoin suspected gingival hyperplasia	Phenytoin suspected gingival hyperplasia
146	20	M	Anti-TB suspected skin pigmentation (blackening)	No ADR suspected
156	35	M	Epigastric pain with unknown agent	No ADR suspected
168	40	M	Nevirapine suspected skin rash	No ADR suspected
172	80	M	Enalapril suspected dry cough	No ADR suspected
212	80	F	Penicillin allergic	No ADR suspected
225	32	F	Co-trimoxazole and nevirapine suspected skin rash	No ADR suspected
257	30	F	Lamivudine suspected vomiting	No ADR suspected
370	35	F	Anti-TB suspected hepatotoxicity	No ADR suspected
380	36	F	Warfarin suspected bleeding	No ADR suspected
776	21	M	Warfarin suspected bleeding	No ADR suspected
785	35	F	Anti-TB suspected unidentified ADR	No ADR suspected
956	48	F	Unfractionated heparin suspected phlebitis	No ADR suspected